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FURTHER EXPERIENCES IN THE USE OF TRANSPLANTED ABDOMINAL FASCIA IN THE RELIEF OF STRESS INCONTINENCE

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INCONTINENCE of urine occurring under circumstances which raise intra-abdominal pressure, such as sneezing, coughing, etc., is a fairly common complaint among gynecologic patients. In many of them this symptom is of minor consequence and often is not admitted unless the patient is directly questioned in regard to her urinary control.[1] The term generally accepted for this condition is that of stress incontinence, said to have been coined by Eardley Holland.[2] It has also been called diurnal incontinence,[3] but less aptly since, while it occurs most commonly during the daylight hours, it is related directly to effort on the part of the patient.

While in the majority of instances this symptom is so slight that it constitutes only a minor annoyance, it sometimes develops to such a degree that the patient, on the slightest muscular effort, discharges large quantities of urine. Such individuals are only continent when lying down or sitting quietly and, even under these circumstances, as can be readily demonstrated on the examining table, there is lack of urinary control if the intra-abdominal pressure is raised. It is with this extreme degree of stress incontinence, particularly if previous surgical efforts at relief have failed, that this report is chiefly concerned.

The etiological factors in the background of this condition are well known, consisting most commonly of the injuries which occur to the supporting structures of the pelvic organs during the process of parturition. If such injury is concentrated on the supporting tissues of the bladder neck and upper urethra, stress incontinence will appear immediately (Refer to Case 2, Group II). On the other hand, if the injury is mostly to the supporting structures of the posterior part of the bladder trigone the symptom may not appear until many years later, usually at about the time of the menopause. This is the most common sequence of events.

The involutionary changes at the menopause have a marked influence on the development of this symptom, and sometimes, in nulliparous women, appear to be solely responsible for its appearance. It has long been known that spayed female dogs exhibit urinary incontinence, and veterinary surgeons were the first to point out that this disorder could be controlled by the administration of stilbestrol. Geist and his co-workers[4] have reported on the beneficial effects of estrogen therapy in human subjects exhibiting urinary symptoms during the menopause. Case 4, Group I, illustrates the advantages as well as the disadvantages of this form of treatment for stress incontinence. Finally, in rather rare instances, individuals are encountered who give a history of stress incontinence since early childhood. Their disability usually is increased to a marked degree by parturition. Case 1, Group II, illustrates this rather uncommon background. A congenital weakness in the supporting structures must be assumed in these patients. The etiological factors therefore may be traumatic, involutional or hormonal, congenital, or a combination of two or more of these factors.

The physical characteristics of women suffering from severe stress incontinence are surprisingly similar. In order to prevent urinary leakage, they avoid physical activity as much as possible, and, therefore, tend to become adipose and flabby. This tendency does not improve their risks as surgical patients. As a rule it cannot be improved before operation. Only by relieving the patient of her disability can she be made more active, with a resultant improvement in her general condition.

Pelvic examination may reveal a variety of lesions due to injury or relaxation of the pelvic supporting structures. In addition, other gynecologic conditions, such as uterine fibroids, may be present. However, the lesion which is essentially associated with the symptom is the urethrocele. This is exemplified by the patients in whom previous surgery has given excellent results as far as the general pelvic supporting structures are concerned, but in whom the urethrocele alone recurs, associated with a continued lack of urinary control. This is illustrated by six of the seven cases to be presented in Table I. An uncomplicated urethrocele often escapes casual examination, the bladder and urethra appearing to be well supported. On requesting the patient to cough or strain, a typical displacement takes place; the bladder neck and upper urethra bulge downward with the lower vaginal wall, which rotates through an arc whose center is at the lower border of the symphysis, so that the urethral orifice points upwards and forwards. At the height of this movement a thick stream of urine is ejected with considerable force, sometimes for several feet. Bonney[2] has pointed out that the escape of urine can be prevented by placing a finger on each side of the bladder neck and holding it behind the symphysis. He offers this as a test to determine whether a successful result can be attained by surgery. A sound placed in the urethra further aids in demonstrating the degree to which the upper urethra and bladder neck can be displaced backward and downward from behind the symphysis. Cystoscopic examination yields little information. With the patient reclining and at rest, no abnormalities of bladder capacity can be found. The usual "waterfall effect" at the internal urethral orifice is absent, indicating a loss of tone in the sphincter. On straining, the anterior part of the trigone will be seen to fall backward and downward, producing a cone-shaped urethral orifice. The significance of this finding will be discussed later.

To understand the lesion which constantly accompanies stress incontinence, a brief review of the supporting mechanism of the female urethra and bladder is necessary. The trigone of the bladder rests upon a sheet of tissue which separates it from the anterior vaginal wall. This sheet is composed of areolar tissue, in which are embedded nonstriated muscle fibers running in an anteroposterior direction. Because of its gross characteristics it is called the pubocervical fascia, although it differs microscopically from the structure of true fascia. It is attached, in front, to the back of the symphysis and behind, in the midline, to the cervix at its junction with the vagina, while on each side it blends with the corresponding transverse cervical ligament. Laterally, it can be traced upward to the pelvic side wall where it is attached along the white line, which is the line of fusion of the visceral and parietal layers of the endopelvic fascia.

The pubocervical fascia is separated from the base of the bladder by a plane of cleavage, which is utilized in separating the vagina from the bladder in complete hysterectomy. Any weakness in the posterior part of this sheet can be demonstrated and repaired during this operation. The inferior aspect of this sheet lies against the anterior vaginal wall, a plane of cleavage intervening which is made use of in the repair of systocele. It is perforated at its anterior extremity by the urethra to which it contributes a sheath of tissue which surrounds this structure in its downward course, and which, when traced laterally, attaches itself to the back of the lower pubic body. The bladder itself receives an investing layer of fascia derived from the superior aspect of the pubocervical layer. It is along the line of cleavage between this investing layer of fascia and the bladder muscularis that the peritoneum is freed from the vesicle fundus in the Waters extraperitoneal cesarean section. The anterior aspect of the bladder with its covering of fascia is attached to the back of the pubic bone only by thin fibers. It can be separated from the bone with great ease down to the attachment of the pubocervical sheet, where immediate resistance is met because of the firm attachment of the latter to the bone.

It seems evident that the lesion permitting the development of urethrocele must consist in the sudden tearing or gradual attenuation of the most anterior part of the pubocervical fascia, together with its descending investment on the urethra, thus allowing the bladder neck and urethra to herniate downward and backward through the defect. Cystoscopic observation suggests that the posterior segment of these structures is mainly involved. Whether there is associated injury to the inner and outer longitudinal and middle circular muscle layers of the urethra and to the internal sphincter is a matter of controversy. Some students of this condition, notably Kelly,[12] maintain that the incontinence is due to injury of the intrinsic muscles of the upper urethra and bladder neck, while others, notably Watson[1] and Bonney,[3] maintain that the intrinsic muscles in these regions, having lost their fibromuscular support, tend to lose tone and to become ineffective. Kennedy[5-7] has recently conducted an extensive investigation of the intrinsic musculature of the urethra and bladder neck by an ingenious contrivance, and finds extensive alterations in the contour of the urethra and the bladder neck, when stress incontinence is present; he assumes that this must be due to changes in the intrinsic muscles. He concludes, however, that the most important factor in the defect is the injury to the supporting mechanism which allows the musculature to become ineffective. The bulk of evidence points to the fact that the intrinsic musculature of the urethra and the bladder neck

play only a secondary part in the production of stress incontinence. The primary factor is injury or attenuation of the supporting fascia.

In order to understand the relationship of urethrocele to the symptom of stress incontinence, it is necessary to review the modern concept of the normal mechanism of urination.[8-10] It is no longer believed that this mechanism consists of the simple reciprocal contraction of the detrusor muscle and relaxation of the internal sphincter. It is generally held that the mechanism is more complicated, the action of the circular muscle about the internal urethral orifice being overcome by the strong contraction of the trigonal muscle, which pulls the posterior segment of the orifice upward and backward. This action, coupled with the contraction of the detrusor muscle and assisted by the voluntary efforts of the abdominal muscles, effects the passage of urine. This muscle, known as Bell's muscle, is derived from the inner longitudinal muscle layer of the ureters and, spreading laterally to form the prominence known as the interureteric ridge, and downwards and medially toward the urethra, is responsible for the elevation of the trigone above the level of the adjacent portions of the bladder. The anterior fibers of this muscle pass into the posterior urethral wall internal to the circular layer of the internal sphincter. It can readily be seen that its contraction exerts a posterolateral force pulling the posterior segment of the orifice open. In the normal woman the entire trigonal area is fixed and firmly supported by the pubocervical fascia, which adequately resists increases in abdominal pressure. The internal urethral orifice does not come under the influence of any other force than the backward and upward pull of the trigonal muscle.

With the development of a urethrocele consequent on injury to or inadequacy of the supporting tissue, the sphincter mechanism becomes subject to additional forces. Even the slightest increase of intra-abdominal pressure must cause some movement downward and backward of the anterior trigone. This constant tug on the circular muscle of the internal sphincter results in its loss of tone. When sharp increase of intra-abdominal pressure takes place, the anterior trigone herniates through the defect, pulling open the posterior segment of the internal orifice by overcoming the internal sphincter. This accounts for the cystoscopic observations on patients with urethrocele. The resultant incompetence of the internal sphincter accounts for the sudden escape of urine, under the propulsion of the increased intra-abdominal pressure and the normal tone of the detrusor muscle. When intra-abdominal pressure falls, the trigone rises, releasing the internal sphincter, which once more becomes competent. This appears to be the mechanism by which stress incontinence is produced and closely approximates that offered by Taylor and Watt[11] in 1917.

It is beyond the scope of this paper to discuss in detail all the surgical procedures that have been employed in the treatment of stress incontinence. While Kelly[12] believed that the fundamental weakness lay in the internal sphincter, and devised an operation, popularly known as the "Kelly stitch" for tightening this muscle, most students of this disorder today believe that the essential weakness lies in the supporting structures about the upper urethra and bladder neck. The success attained by Kelly is attributed to his unconscious inclusion of these tissues in his repair. While some operators[13] plicate the dilated urethra and bladder neck before approximating the supporting fascia, others[1, 3] believe that this is unnecessary because the urethra and bladder neck rapidly regain tone and normal dimensions once proper support is attained. Other operators[14] have

stressed the importance of repairing the external sphincter and the advancement of the urethral meatus,[15] although the manner in which the lower third of the urethra can take part in the production of stress incontinence is not clear. Kennedy,[7] as a result of his recent investigations, advocates a very wide dissection of the urethra and bladder neck. The fascia is freed to its attachment to the pubic bone, from which it is separated, so that the urethra is completely mobilized. The redundant urethra and bladder neck is plicated by interrupted sutures and the supporting fascia closely approximated over this layer by additional interrupted sutures. The external sphincter is approximated in addition. He places great emphasis on the freeing of adhesions between the urethra and the back of the pubis. These he believes are important factors in the incontinence. He has reported excellent results, as has Counsellor,[16] who has followed his technique.

The postoperative results of these procedures have been in the main successful. Few reports, however, equal that of Kelly,[12] who, in 1913, stated that he had been using his procedure for ten to twelve years and had yet to encounter a failure. Most observers who have followed up their cases report a considerable incidence of partially or totally unsuccessful results. Shortly after Kelly's initial article, he reported with Dumm[17] on a series of twenty cases with complete failure in four, or 20 per cent. Watson[1] reported 105 cases with successful results in 65.7 per cent, partial relief in 21.9 per cent, and failure in 12.4 per cent. Furniss,[18] reporting on twenty-one cases, states that of the seventeen patients followed up thirteen were relieved, two were improved, and two were complete failures (12.9 per cent). His failures occurred in patients with an extreme degree of stress incontinence. Kennedy[7] reporting on twenty-eight cases, states that two failures occurred, an incidence of 7.1 per cent; Bonney,[3] while not giving percentages, states that he has failed to achieve surgical cure in some patients. Davies[19] reports 8 per cent failures in a series of 100 cases.

If the facts underlying this condition which have been presented are correct, there are three possible explanations of these failures: first, that the operative procedure has been inadequate; second, that the healing process has been imperfect due to infection or faulty blood supply; and third that the supporting tissues utilized in the repair are so attenuated that they once more give way under the continual assault of intra-abdominal pressure. The first explanation can be discarded since the failures enumerated above have occurred in the hands of experienced operators, most of whom utilized procedures which appear fundamentally correct. Of the second and third explanations, the last appears the most likely since serious infection is rarely seen in operations on the anterior vaginal wall, and in most of the failures, temporary relief is obtained only to be followed by a recurrence of the condition.

If the original supporting structures are so attenuated as to be of no further value, the possibility of transplanting tissue from another source should be considered. This is by no means a new idea.

In 1910, Goebell[20] reported on the transplantation of the pyramidalis muscles, attaching their free ends about the neck of the bladder. In 1914 Frangenheim[21] modified this technique by utilizing, in addition to the pyramidalis, strips of the overlying fascia, and included sometimes part of the rectus muscle. In 1917 Stoeckel[22] advised the addition of a vaginal plastic operation to the above procedure. In 1907 Giordano[23] described the use of the transplanted distal end of the gracilis muscle in cases of stress incontinence. In 1911 Squier[24] and in 1918 Taussig[25] recommended the use of the levator muscles. In 1923 Thompson[26] transplanted strips of rectus muscle and fascia downward in front of the pubic bone and sutured them about the lower urethra. Miller[27] reported on a somewhat similar procedure in 1932. In 1929, Martius[28] described the transplantation of the bulbocavernosus muscle and its surrounding fat in between the urethra and the vagina. In all of these techniques it is to be noted that the substitution of voluntary muscle for a supposedly injured internal sphincter

was considered to be of more importance than the restoration of proper support. This probably accounts for some of the failures which followed the use of these procedures. It is doubtful, moreover, if voluntary muscle will survive in its transplanted condition owing to defects in its nerve and blood supply, and to altered function. One such case has been reoperated in which the voluntary muscle was found to be changed to dense, almost cartilaginous, connective tissue. In 1933 Price[29] reported on a case in which he had utilized a strip of fascia lata passed under the urethra by the suprapubic route. The ends of the strips were attached to the rectus muscles on each side; a successful result was attained. Aldridge[30] in 1942 reported on the use of transplanted strips obtained from the aponeurosis of the oblique muscles in combination with a plastic operation on the bladder neck and upper urethra. He had obtained complete relief in a patient with stress incontinence who had been operated upon twice before without success. This technique in a somewhat modified form has been utilized by me in a number of cases, four of which have been reported previously.[31] While caring for these patients, further applications of the same principle have been developed. Experience gained in the use of transplanted abdominal fascia in combination with vaginal plastic operations upon the upper urethra and bladder neck in patients suffering from urethrocele and stress incontinence form the basis for this report.

Technique

The technique utilized in patients with previous operative failures may be described as follows:

Procedure 1.—The patient is put in the dorsal position and the lower abdomen is prepared with merthiolate and draped with towels. The area exposed should include the upper border of the symphysis and both anterior superior iliac spines. A long incision is made with its center about 2 to 3 cm. above the upper border of the symphysis and curving upward on each side of the midline to a point slightly above the anterior superior iliac spines. It extends through skin and fat down to the aponeurosis of the external oblique and the external rectus sheath. The aponeurosis at the bottom of the incision is carefully cleansed of fat and all bleeding is controlled with fine catgut ligatures. The aponeurosis of both the external oblique and internal oblique is incised longitudinally with a scalpel for a distance of 1½ to 2 cm. at the lateral extremity of the skin incision. The inner surface of the internal oblique aponeurosis medial to this incision is freed from the underlying muscle. Beginning at each angle of the incision a strip of the combined aponeurosis is mobilized by means of two parallel incisions extending downward and medially to a point about 1.5 to 2 cm. of the midline. As a rule, some fibers of the internal oblique must be separated from the inner aspect of the strip. A similar strip is then obtained from the opposite side.

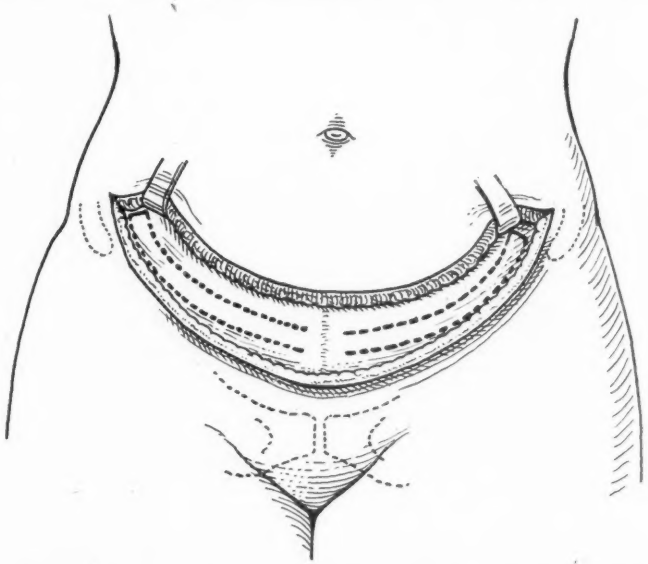

Fig. 1.—Type of abdominal incision utilized in exposing aponeurosis of external oblique and external rectus sheath. The extent of the aponeurotic strips has been outlined.

The attachment of the medial end of each strip is carefully preserved and lies about 1 to 1.5 from the midline (Fig. 1). The defect in the aponeurosis is closed up to the border of the rectus muscle with a running No. 1 chromic catgut suture, care being taken to include both the internal and external layers. Traction sutures are then passed through the tips of the aponeurotic strips and held by small clamps. The strips are then placed in the depth of the incision and the open wound is covered with a sterile towel.

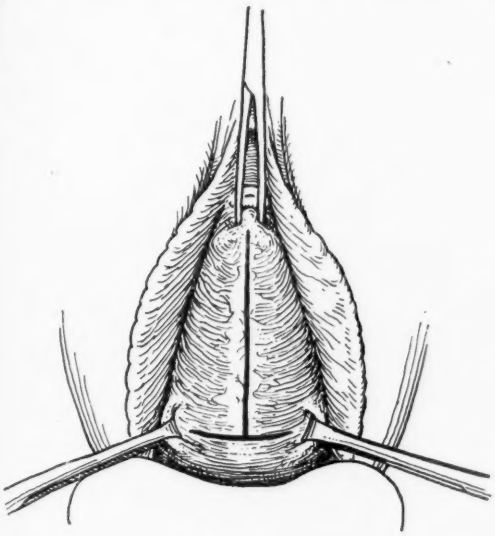

Fig. 2.

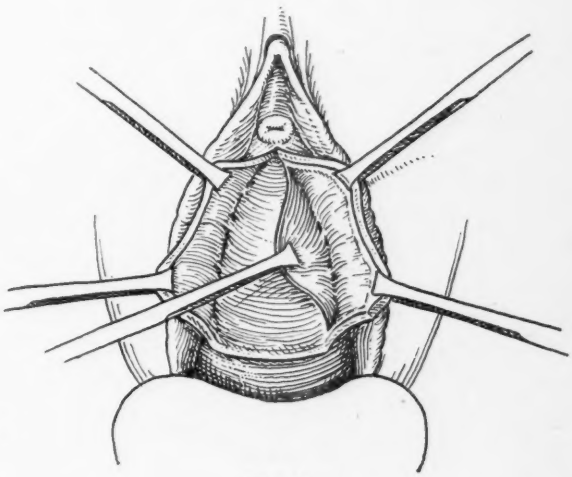

Fig. 3.

Fig. 2.—Inverted T incision over bladder neck and upper urethra. Vaginal wall fixed by means of Allis clamps.

Fig. 3.—Vaginal incision completed and plane between pubocervical fascia and vaginal wall defined.

The patient is now put in the lithotomy position, prepared and draped. The labia minora are retracted laterally by stay sutures. A weighted speculum is placed in the vagina exposing the lower anterior vaginal wall. In most of these patients previous operative procedures have resulted in adequate support to the portion of the bladder adjacent to the upper vagina and cervix. As a result of the previous perineorrhaphy the cervix is difficult to draw down or to expose. Since the necessary dissection is mainly about the upper urethra and bladder neck, such exposure is not necessary. The anterior vaginal wall is seized with two Allis clamps, placed as far lateral to the midline as possible, and at as high a level as can be attained. In the midline there is usually the scar of one or more previous operations. Holding the vaginal wall tensely by lateral traction on the clamps, a transverse incision is made with a scalpel through the depth of the vaginal wall (Fig. 2). Scissor dissection at the lateral portions of this incision defines the plane between the bladder and the vaginal wall, following which the scar in the midline can be divided without any risk of injury to the bladder neck and urethra. The vaginal wall is then divided in the midline at right angles to the incision. This last incision should be carried to a point about 1 cm. from the urethral orifice. The plane of the supporting fascia of the bladder neck and upper urethra is then identified, varying amounts of sharp dissection being necessary (Fig. 3). Once found, the plane of separation can usually be followed by blunt dissection with the finger outward and upward to its line of attachment along the inner aspect of the superior pubic ramus. Moderate pressure at this point with the finger results in rupture of the attachment allowing the finger to enter the space of Retzius (Fig. 4). This dissection is carried out on each side. The bladder neck and upper urethra are thus fully mobilized. Considerable bleeding may accompany the latter stages of this dissection due to rupture of veins about the bladder neck. Since the source of bleeding is inaccessible, it is fortunate that it ceases spontaneously after a short interval. The supporting fascia of the upper urethra and bladder neck is then plicated by means of interrupted mattress sutures. If marked relaxation is present, a second layer of such sutures can be added (Fig. 5).

At this point an assistant removes the sterile cover from the abdominal wound. The operator passes a uterine forceps lateral to the bladder neck along the plane of separation of the supporting fascia, through the defect created in the attachment of this fascia into the space of Retzius. On introducing the clamp further, the tip can be felt through rectus muscle by the assistant working above. Slight additional pressure passes the clamp through the body of the muscle. The traction suture attached to the aponeurotic strip on the corresponding side can then be seized and drawn downward in the reverse direction to which the clamp has been passed, drawing after it the strip itself (Fig. 6). This procedure is repeated on the opposite side. The ends of the strips are then approximated by simply tying the traction sutures together, thus forming a sling about the bladder neck (Fig. 7). This sling should be, and usually is, tight enough to pull the bladder neck well up behind the symphysis. It probably cannot be too tight, but if too loose it may fail to produce a good result. If the sling is accessible after the ligatures are tied, a few interrupted sutures may be added to reinforce its point of union. However, satisfactory healing seems to follow even when the retraction of the sling makes this additional procedure impossible. The vaginal mucosa is then closed with interrupted sutures including, when possible, a bite of the underlying tissue to eliminate dead space. As a rule no vaginal mucosa is removed.

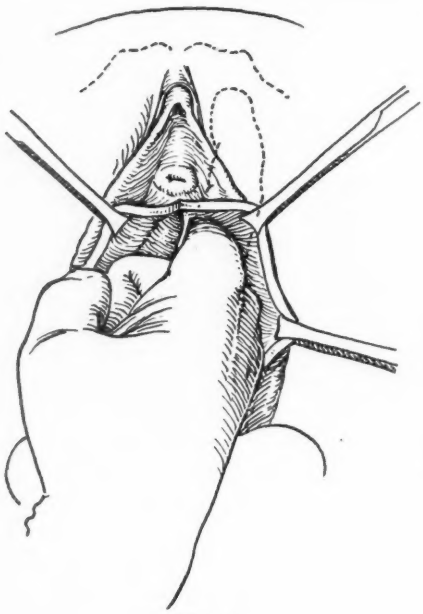

Fig. 4.

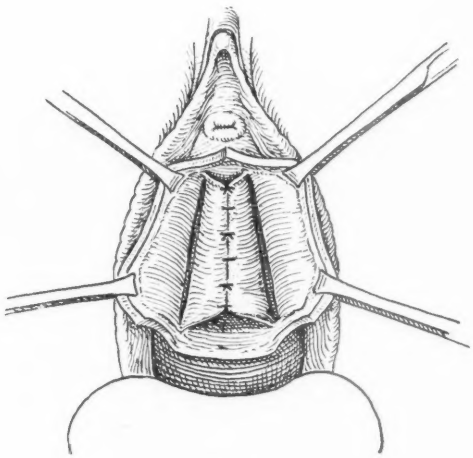

Fig. 5.

Fig. 4.—Plane between pubocervical fascia and vaginal wall followed upward and laterally to pubic attachment. The fascia is ruptured at this point, allowing the finger to enter space of Retizus.

Fig. 5.—The pubocervical fascia has been approximated in front of bladder neck and upper urethra by means of mattress sutures.

In the meantime, the abdominal operator is completing the closure of the abdominal incision. The defect in the lateral portion of the external rectus sheath is closed with continuous chromic suture. The fat is closed with a running plain catgut suture. Rubber tissue drains are placed in the depth of the wound and led out of each angle. Four grams of sulfanilamide powder are dusted into the wound because of the likelihood of contamination by organisms introduced by instruments passed upward from the vaginal tract. The skin is then closed with interrupted dermol sutures. The total time necessary for this procedure in recent cases has amounted to about sixty minutes. A large absorbent dressing should be applied to the abdominal wound because of the rather profuse serosanguineous drainage which takes place in the first forty-eight hours. A self-retaining catheter is placed in the bladder.

The important elements in postoperative care are as follows: The abdominal wound should be dressed and the drains removed about forty-eight hours postoperatively. Sulfadiazine, 0.5 Gm., is administered four times a day until the catheter is removed or until the

patient voids, in order to avoid urinary infection. The catheter is removed about the ninth day, spontaneous voiding of urine occurring sometimes immediately, but usually not until a few days later. Catheterization at eight-hour intervals must be carried out during this time. The skin sutures are removed on the ninth day and the patient is allowed up on the eleventh day. So far no infections have been encountered. While all of the cases about to be reported have not been treated in exactly this fashion, this is the routine that has been adopted as a result of experience.

This procedure has been utilized on ten patients who for purposes of classification may be considered in two groups.

In the first group of seven, all of the patients had been subjected to previous plastic operations for the relief of various degrees of relaxation of the pelvic supports. A total of thirteen operations had been performed on them. All of them, in addition, suffered from severe stress incontinence at the time of their initial operation. In all but one of them (Case 3, Group I) satisfactory results had been attained except for the recurrence of urethrocele and the failure to relieve stress incontinence. In some of them this symptom had become increasingly severe. All of the operations had been carried out by competent gynecologic surgeons. Case 3 in this group, a woman who required both a plastic operation and a hysterectomy, should be kept in mind when the patients in Group III are discussed.

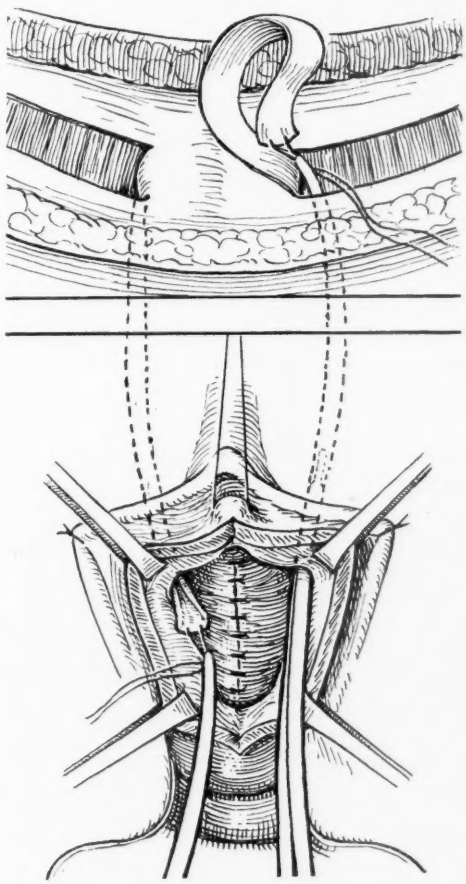

Fig. 6.

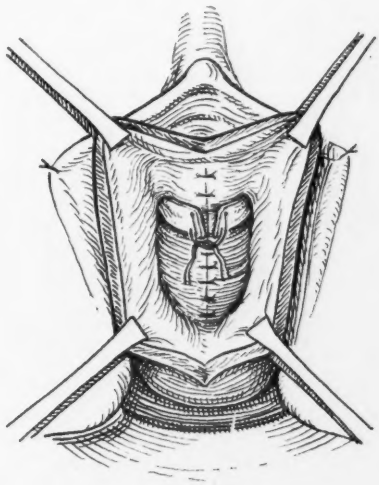

Fig. 7.

Fig. 6.—On the left, uterine forceps has been passed upward between fascia and pubic ramus, through the space of Retzius and the left rectus muscle; it is grasping a traction suture attached to the end of the left aponeurotic strip. On the right, the aponeurotic strip on the corresponding side has been drawn downward by the traction suture in the reverse direction to which the clamp has been passed.

Fig. 7.—The fascial strips are being approximated to form a sling by tying the traction sutures together. This sling should be fairly tight and retracts the bladder neck upward and forward behind the symphysis. Actually, at operation, the bladder neck disappears behind the symphysis so that the sling cannot be seen as depicted by the artist. If accessible, the union of the ends of the strip may be reinforced by interrupted sutures.

TABLE I*A*. PATIENTS IN WHOM PREVIOUS SURGICAL EFFORTS HAVE FAILED

PATIENT	CASE NO.	AGE	PARITY	PRIMARY DIAGNOSIS	PREVIOUS SURGERY	RESULT	REMARKS
(1) B. H.	J. V. 8523-43	38	P. iii G. iv	1930. Cystocele. Relaxed perineum. Stress incontinence, duration 7 years	1930. Repair of cystocele—Kelly stitch. Perineorrhaphy. 1935. Repair of cystocele—Kelly stitch. 1940. Repair of bladder neck and upper urethra—Kennedy technique. 1940. Implantation of fascia lata under bladder neck.	Adequate support to bladder adjacent to upper vagina. Bladder neck and upper urethra fell away from symphysis on straining. Marked stress incontinence	1924. First labor 5 days long. Delivered with low forceps. Beginning of incontinence
(2) B. H.	S. F. 22741-43	42	P. ii G. ii	1942. Cystocele. Relaxed perineum. Stress incontinence, duration 6 years	1942. Repair of cystocele, bladder neck, and upper urethra —Kennedy technique	Adequate support to bladder adjacent to upper vagina. Bladder neck and upper urethra fell away from symphysis on straining. Marked stress incontinence	1932-1934. Nine-pound children. Onset of stress incontinence after second delivery
(3) B. H.	S. T. 22794-43	51	P. iii G. v	1938. Cystocele. Relaxed perineum. Large fibromyomas. Stress incontinence, duration 18 months	1942. Repair of cystocele—Kelly stitch. Perineorrhaphy. Supravaginal hysterectomy. 1939. Repair of cystocele, bladder neck, and upper urethra —Kennedy technique. 1941. Repair of cystocele and interposition of cervical stump	Rapid recurrence of cystocele after each operation. Finally prolapse of vault of vagina and cervical stump. Increasing stress incontinence	1926. Left nephrectomy. Stress incontinence appeared in 1940 long after birth of last child in 1919

(4) S. H.	S. W. 638395	55	P. iii G. iv	1941. Slight cystocele. Urethrocele. Stress incontinence, duration 1 year	1942. Repair of supporting fascia about bladder neck and upper urethra	Slight improvement for few weeks after operation. Stress incontinence then returned. Anatomic result good. Urethrocele	Stilbestrol 1 mg. o.d. controlled incontinence. Produced profuse uterine bleeding, requiring curettage
(5) S. H.	M. C. 331479	69	P. iii G. iii	1939. Cystocele. Rectocele. Complete prolapse of uterus. Small fibromyoma. Stress incontinence, duration 3 years	1939. Curettage. Repair of cystocele. Amputation of cervix. Repair of rectocele and perineum	Excellent result as far as support of bladder, uterus and rectum were concerned. Stress incontinence reappeared Jan., 1941. Became progressively worse. Urethrocele	Stress incontinence appeared to be related to development of prolapse after menopause
(6) S. H.	T. M. 759958	50	P. iii G. iv	1941. Cystocele. Relaxed perineum. Stress incontinence, duration 3 years	1941. Repair of cystocele and urethral sphincter. Perineorrhaphy	Adequate support to bladder adjacent to upper vagina. Bladder neck and upper urethra fell away from symphysis on straining. Marked stress incontinence. Urethrocele	
(7) S. H.	R. C. 225197	50	P. vii G. xii	1932. Cystocele. Rectocele. Early pregnancy. Stress incontinence	1932. Vaginal sterilization. Therapeutic abortion. Repair of cystocele, rectocele and perineum. 1933. Repair of fascial supports about bladder neck and upper urethra	Excellent result after first operation except for bladder neck and upper urethra. Stress incontinence continued. Improvement and gradual recurrence of incontinence after second operation. Urethrocele	Incontinence appeared after eleventh pregnancy. Baby born as O.P., spontaneous. No lacerations. Wt. 3350 Gm.

TABLE I*B*. PATIENTS ON WHOM PREVIOUS SURGICAL EFFORTS HAVE FAILED

PATIENT	CASE NO.	PREOPERATIVE DIAGNOSIS	OPERATION DATA	POSTOPERATIVE COURSE	FOLLOW-UP
(1) B. H.	J. V. 8523 1943	Urethrocele. Stress incontinence	9/ 5/43. D. & C. Procedure 1	Uneventful. No infection. Catheter accidentally removed on 4th day. Not replaced because spontaneous voiding occurred	9/ 6/43. Perfect urinary control. 12/15/43. Slight leakage on going out into cold air. Also when loses temper with children. 10/ 2/44. Condition same. Anatomic result good
(2) B. H.	S. F. 22741 1943	Urethrocele. Stress incontinence	5/15/43. D. & C. Episiotomy. Procedure 1	Uneventful. No infection. No retention catheter used. Voided immediately without trouble	12/ 6/43. Urinary control perfect. 7/16/44. Urinary control perfect. Excellent anatomic result. Feels tug at bladder neck on coughing.
(3) B. H.	S. T. 22794 1943	Urethrocele. Cystocele. Prolapse of cervical stump and vagina Stress incontinence	5/13/43 Extensive plastic excision of cervical stump. Procedure 1	Gradual anuria due to occlusion of right ureter by edema. Relieved by right nephrostomy 5/17/44. Normal urination gradually re-established. No infection	12/ 4/43. Perfect urinary control. 7/16/44. Perfect urinary control. Slight cystocele. Otherwise good anatomic result
(4) S. H.	S. W. 638395	Urethrocele. Stress incontinence	4/ 7/44. D. & C. Procedure 1	Uneventful. No infection. Catheter removed on 10th day. Spontaneous voiding	5/16/44. Perfect urinary control. 9/23/44. Perfect urinary control. Good anatomic result. Slight pain at left angle of abdominal incision. No hernia
(5) S. H.	M. C. 331479	Urethrocele. Stress incontinence	7/18/44. D. & C. Episiotomy. Procedure 1	Uneventful. No infection. Catheter pulled out 2nd day. Spontaneous voiding 8th day	9/23/44. Perfect urinary control. Excellent anatomic result
(6) S. H.	T. M. 759958	Urethrocele. Stress incontinence	10/ 3/44. D. & C. Procedure 1	Uneventful. No infection. Catheter out on 9th day. Spontaneous voiding	11/30/44. Perfect urinary control. Excellent anatomic result
(7) S. H.	R.C. 225197	Urethrocele. Stress incontinence	10/10/44. D. & C. Procedure 1	Fever 103.6° first day. Subsided rapidly. No infection. Catheter out on 9th day. Voided spontaneously	11/30/44. Perfect urinary control. Excellent anatomic result

TABLE II. PATIENTS IN WHOM PROCEDURE 1 WAS USED AS INITIAL OPERATION

PATIENT	CASE NO.	AGE	PARITY	DIAGNOSIS	OPERATION	POSTOPERATIVE COURSE	FOLLOW-UP	REMARKS
(1) S. H.	M. T. 716559	45	P. ii G. iii	Cystocele, urethrocele. Relaxed perineum. Rectocele. Right Bartholin cyst. Stress incontinence—life	8/ 4/43. D. & C. Plication of fascia beneath bladder and upper urethra. Transplantation of abdominal fascia. Repair of rectocele and perineum. Excision of Bartholin cyst	Fever 102° F., 1st day P.O. Otherwise uneventful. Catheterized until 12th day before spontaneous voiding began. No infection	12/ 8/43. Perfect control of urination. 9/20/44. Perfect control of urination. Slight weakness left outer angle of abdominal wound	Stress incontinence since childhood. Much worse after pregnancies
(2) S. H.	A. S. 483911	36	P. i G. ii	Urethrocele. Stress incontinence, 8 years, becoming progressively worse	7/28/44. D. & C. Plication of fascia of bladder neck and upper urethra. Transplantation of abdominal fascia	Uneventful. No infection. Catheter removed 12th day. Frequent painful urination for few days	9/23/44. No stress incontinence. Urgency after 3 hours. Anatomic result good	Had normal labor at term. Baby, 3,270 Gm. No lacerations.
(3) S. H.	M. K. 684430	60	P. ii G. ii	Urethrocele. Stress incontinence, 1 year	10/27/44. Plication of fascia of bladder neck and upper urethra. Transplantation of abdominal fascia	Uneventful. No infection. Catheter out 9th day. Unable to void for several days	11/30/44. No stress incontinence. Nocturnal frequency. No evidence of urethrocele	Vaginal hysterectomy and plastic in 1940 for prolapse. Excellent result except for urethrocele

Table I*A* summarizes the important facts in the past history of the patients in this group.

Table I*B* summarizes the condition present following the previous surgical failures, the type of operation utilized, the postoperative course, and the follow-up observations in this group.

When this technique was first attempted, it was resolved that it should be confined to patients in whom previous surgical efforts had failed. The apparently successful results attained in the initial cases seemed to warrant its application as a primary procedure in those patients whose stress incontinence seemed to be so marked or whose tissues appeared of such poor quality that the usual repair of the normal fascial supports appeared foredoomed to failure. Those patients, three in number, constitute Group II.

Table II summarizes the important facts in regard to the patients in this group.

While studying these patients, another variety of case was encountered in which a different operative technique was indicated. These patients had multiple complaints and required both plastic and abdominal surgery.

For certain details of the procedure utilized in these patients, indebtedness must be expressed to Meigs,[32] who has used a similar operation. It can be described as follows:

Procedure 2.—The dissection about the bladder neck and upper urethra is carried out exactly as has been outlined under the first procedure. However, after the supporting fascia has been plicated by means of interrupted mattress sutures, the vaginal mucosa is closed by interrupted sutures, great care being taken to avoid the inclusion of any of the underlying tissue (Fig. 8). As a result there is left a U-shaped space encompassing the upper urethra and bladder neck, both arms of the U terminating in the space of Retzius. A retention catheter is placed in the bladder.

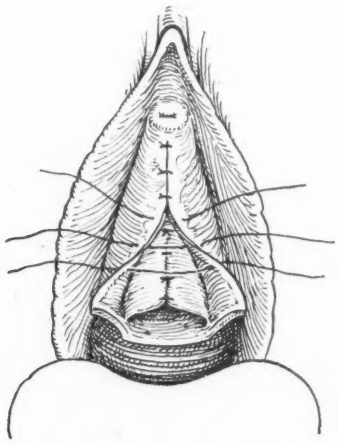

Fig. 8.—Exactly the same type of dissection has been carried out about the upper urethra and bladder neck as has been described in Procedure 1. The vaginal incision is closed, taking care that none of the underlying tissue is included. A U-shaped space is left embracing the bladder neck, the arms of the U terminating in the space of Retzius.

The patient is then put in the dorsal position, prepared with merthiolate and draped. A long, suprapubic midline incision is made, curving to the right of and extending slightly above the umbilicus. The abdominal wall is opened in layers. The medial portion of the external rectus sheath is freed from fat to a width of 1.5 cm. (Fig. 9.) The wound is draped with towels and clips, and the peritoneum opened. After exposing the pelvic organs with a retractor and packing off the intestines into the upper abdomen by means of pads, a complete hysterectomy is carried out, the ovaries and tubes being left or removed as indicated. Before closing the vagina any defect in the pubocervical fascia beneath the upper bladder can be repaired by identifying the stronger, lateral portions of this structure and uniting them by interrupted sutures between the bladder and vagina. The vagina is then closed and all raw surfaces peritonealized in the usual way. The pads and retractors are removed and the peritoneum of the abdominal incision is closed.

A strip, 1 cm. wide, is cut free from the inner margin of the right external rectus sheath, beginning at the upper end of the wound and extending to within 2 cm. of the lower end where its attachment is preserved. This strip should be as long as possible since one

can always get rid of excess tissue. On the other hand, too short a strip is a handicap that cannot be overcome. Great care must be taken in separating the rectus sheath from the underlying muscle at the linea transversae, one of which is always found close to the umbilicus and sometimes another 2 to 3 cm. below it. The muscle is closely attached to the sheath at these points, and unless the separation is carefully made the fascial strip will be weakened enough to break on moderate traction. Having freed the strip, a traction suture is passed through the tip and tied. (Fig. 10.)

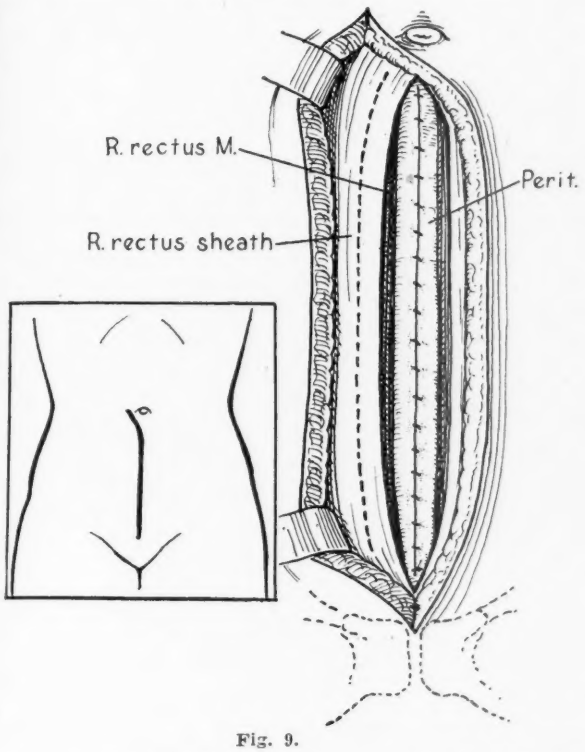

Fig. 9.

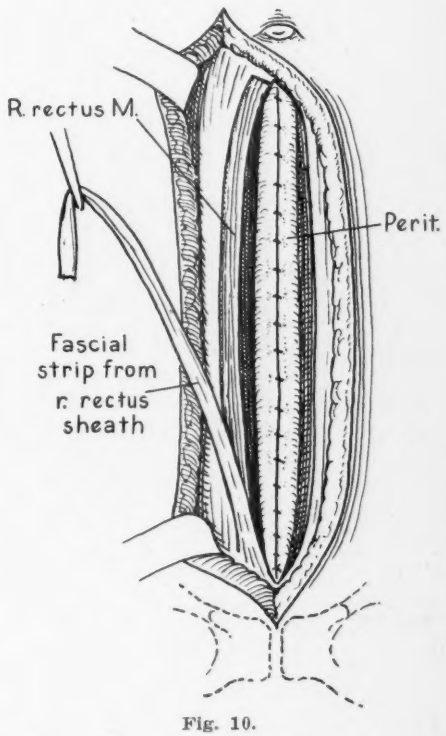

Fig. 10.

Fig. 9.—Inset shows type of incision. Larger drawing shows exposure of external surface of medial portion of right external rectus sheath. The strip to be freed has been outlined. The complete hysterectomy has been carried out and the peritoneum has been closed.

Fig. 10.—The strip has been freed from the median border of the right rectus sheath, leaving the lower end attached.

The anterior wall of the bladder with its pad of fat can now be separated from the posterior aspect of the symphysis. The opening in the prevesical fascia near its attachment to the pubis, made in the dissection of the upper urethra and bladder neck, can be easily identified by an exploring finger. The traction ligature attached to the fascial strip is now threaded on an aneurysm needle, which is passed from right to left, beneath and around the bladder neck, through the U-shaped space left by the previous dissection (Fig. 11). The ligature is seized as it emerges from the left opening of the tunnel, the aneurysm needle is withdrawn, and the attached fascial strip is drawn through the tunnel. The strip is pulled tight enough to bring the bladder neck well up to the back of the symphysis and is then secured by several interrupted No. 1 chromic catgut sutures to the outer aspect of the left external rectus sheath, opposite its attached end on the right side (Fig. 12). Any excess fascia is excised. A cigarette drain is placed in the space of Retzius and 4 Gm. of powdered sulfanilamide are dusted in this area because of the potential danger of infection from the preceding vaginal dissection. The abdominal wall is then closed in layers, care being taken to leave sufficient space at the lower angle to permit free drainage from the retropubic area.

Postoperatively, the patient is given sulfadiazine, 0.5 Gm. four times a day, until the catheter is removed or until spontaneous voiding occurs. The abdominal drain should be gradually shortened but not completely removed until the fourth day, because of the con-

TABLE III. PATIENTS REQUIRING ADDITIONAL ABDOMINAL SURGERY. PROCEDURE 2

PATIENT	CASE NO.	AGE	PARITY	CHIEF COMPLAINTS	DIAGNOSIS	OPERATION	POSTOPERATIVE COURSE	FOLLOW-UP
(1) S. H.	I. L. 676835	50	P. ii G. ii	Abdominal pain. Abdominal enlargement. Stress incontinence, 6 months	Urethrocele. Slight cystocele. Rectocele. Chronic cervicitis. Fibroids	4/14/44. Procedure 2. Repair of rectocele and perineum. Bilat. salpingo-oophorectomy	Uneventful. Drain out 2nd day. Slight febrile until 9th day. No infection. Catheter out on 6th day. Voided 11th day	7/13/44. Perfect control of urination. Anatomic result excellent. 11/15/44. Same findings
(2) S. H.	O. M. 742209	48	P. ii G. iv	Menorrhagia. Dysmenorrhea. Stress incontinence	Urethrocele. Cystocele. Slight rectocele. Relaxed perineum. Fibroids	6/ 2/44. Procedure 2. Repair of rectocele and perineum. Bilat. salpingo-oophorectomy	Uneventful. Drain out 3rd day. Slight febrile until 10th day. No infection. Catheter out 9th day. Voided spontaneously 10th day	7/13/44. Perfect control of urination. Anatomic result excellent. 11/15/44. Same findings
(3) S. H.	F. W. 751519	43	P. iii G. iii	Metrorrhagia. Pelvic pressure. Stress incontinence	Urethrocele. Retroversion. Fibroid. Relaxed perineum	7/14/44. Procedure 2. Perineorrhaphy	Febrile postoperative course. Drain removed 2nd day. Sutures removed 10th day. Small amount of brownish odorless fatty fluid from lower angle. 11th day clean wound disrupted with discharge of large amount of similar fluid. Secondary repair on 18th day. Discharged on 31st day. Catheter out 9th day. Spontaneous voiding on 12th day	9/23/44. No stress incontinence. Has urgency after 3 to 4 hours. Weakness at lower angle of abdominal wound. Hernia?

siderable discharge of liquefied fat and serosanguineous fluid from the space of Retzius. The retention catheter is removed on the ninth day and the abdominal sutures on the tenth day, following which the patient may be allowed out of bed. Spontaneous voiding may occur immediately but sometimes is delayed for a few days. Periodic catheterization is necessary during this time.

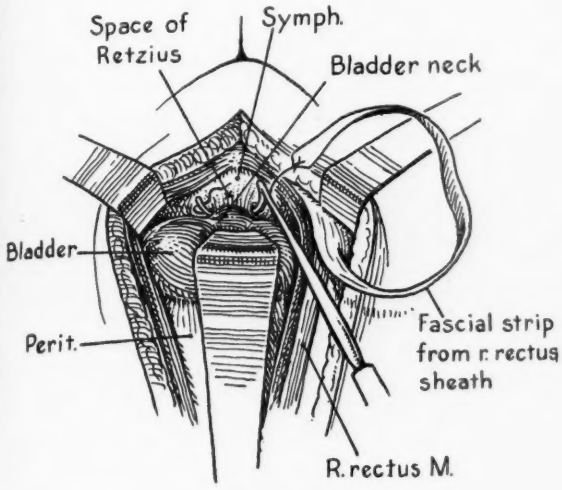

Fig. 11.

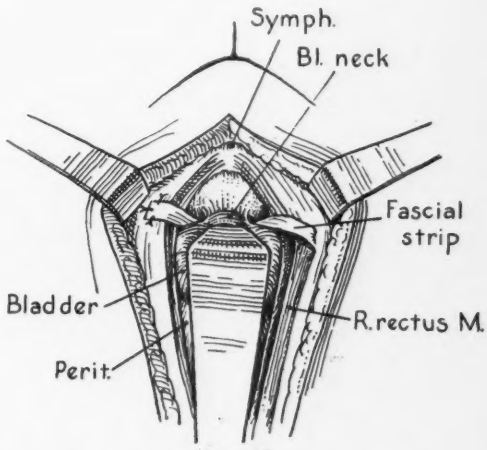

Fig. 12.

Fig. 11.—The bladder has been freed from the posterior aspect of the pubis, and the lateral opening in the pubocervical fascia, made during the vagina dissection, has been identified. A traction suture attached to the end of the fascial strip is being passed about the bladder neck from left to right through the U-shaped space by means of an aneurysm needle.

Fig. 12.—The aneurysm needle has been withdrawn and the fascial strip has been drawn through the space by means of the traction suture. It has been attached to the outer aspect of the left external rectus sheath by several interrupted sutures. The sling thus formed should be tight enough to hold the bladder neck behind the symphysis. Excess fascia may be excised.

This alternative technique has been carried out as a primary procedure on three patients. All of them, in addition to showing various degrees of pelvic relaxation and associated stress incontinence, were found to have uterine fibroids, which produced menorrhagia, metrorrhagia, or pressure symptoms.

Table III shows the important clinical facts in regard to this third group of patients.

Case 3 deserves special mention because of the postoperative course. It is believed that an insufficient exit was left in the lower rectus sheath and that the drain was removed too early. The broken-down fat and serum then dissected upward between the rectus muscles, resulting in the disruption of a wound which showed no gross evidence of infection. On this experience is based some of the precautions mentioned in the description of the operative technique and postoperative care. It is believed that this complication can be avoided in the future by proper attention to adequate drainage of the space of Retzius.

Thirteen patients, suffering from stress incontinence, have been operated upon. In all of them the normal supporting tissues of the upper urethra and bladder neck have been dissected free and plicated beneath these structures. This repair has been reinforced by the formation of a fascial sling obtained from the aponeurosis of the abdominal wall by one of the two procedures which have been described. Although ten of the thirteen patients (Groups I and II) represent cases in which perfect results would seem unlikely if more orthodox procedures had been employed, failure to relieve stress incontinence has yet to be observed. The value of the procedure to patients in Group III cannot be so strongly emphasized, since it is possible that equally good results might have been attained by the usual form of vaginal plastic followed by supravaginal hysterectomy. That the latter type of procedure is open to failure is shown by Patient 3, Group I, whose initial operation was of this variety. The permanence of the results obtained cannot be fully judged as yet. Only eighteen months have elapsed since the first patient was operated on by this type of procedure. It is felt that at least five years with freedom from stress incontinence must elapse before a permanent cure can be assumed.

Some explanation must be offered for the effectiveness of this operation. It is believed the initial plastic repair of the residue of the normal supports of the upper urethra and bladder is of great importance, since, in performing it, these structures are mobilized from the adjacent vagina and from the pubic rami and elevated to a certain extent behind the symphysis. The formation of the fascial sling further elevates and fixes the bladder neck behind the symphysis, and, in healing, reinforces the vulnerable area in the anterior portion of the pubocervical fascia, at which recurrence of the urethrocele can take place. It has been suggested that the sling may cause a kink or stricture of the upper urethra but no evidence of the latter is present on catheterization or cystoscopy of these patients after their operations. In all but one, the voiding mechanism appears to be perfectly normal. In the one exception, Case I, Group II, urination takes place in two installments, separated by an interval of a few seconds. Aldridge,[30] in his original report, postulated that tightening of the abdominal muscles as on coughing and sneezing pulled the sling upward, compressing the bladder neck and thus preventing incontinence. This explanation predicates a rather marked degree of mobility in the sling once full healing has taken place, a condition which would seem most unlikely. In fact, only one of the patients reported above states that she has any sensation in the region of the bladder on coughing or straining. Patient 2, Group I, however, states that she is aware of a distinct tug in the region of the bladder neck. It seems more likely that the chief value of the fascial sling is twofold. In the immediate postoperative period, it fixes the bladder neck at a high level; its attached extremities preserve the vitality of the tissue because of their circulatory connections. Completely detached strips of fascia lata transplanted under the bladder neck, a procedure attempted by the late Frank Sovak and myself, uniformly undergo necrosis and slough out (see Case 1, Group I, Table I*A*, Operation No. 4). The unavoidable secondary infection in vaginal plastic operations may be a factor in the destruction of completely transplanted tissue. The value of the fascial sling in the remote postoperative period lies in the fact that when it is fully healed and incorporated in the undersurface of the anterior pubocervical fascia, the resultant support to the anterior trigone is so strong that it is impossible for the urethrocele to recur. If this explanation is true, the value of the abdominal attachment of the sling is negligible in so far as its traction mechanism is concerned. It is believed that it could be divided from its attachment to the rectus sheath without impairing the control of urination in a patient who suffered from symptoms in the postoperative period attributable to tightness of the sling.

Summary and Conclusions

1. The anatomic basis for urethrocele and its associated symptom, stress incontinence, has been reviewed and discussed, together with the etiological factors which produce this condition.

2. The common type of surgical repair has been reviewed, calling attention to the incidence of failure attendant upon it. Failure appears to be related to the attenuated character of the residual supporting tissue.

3. The use of transplanted tissues has been reviewed, and attention drawn to the faulty concept when voluntary muscle is used.

4. Two methods, utilizing strips of abdominal aponeurosis in addition to plastic repair of the supports of the upper urethra and bladder neck, have been described.

5. Thirteen cases are reported in which these procedures have been used. Close follow-up has so far not revealed a recurrent urethrocele or the reappearance of stress incontinence.

6. The basis for the results attained by these procedures has been discussed:

7. It is believed that these procedures are especially adapted to patients in whom the repair of the normal supports has failed to achieve a good result. In addition, it is believed that, by careful selection, these procedures may be applied as a primary operation in certain cases.

References

1. Watson, B. P.: Brit. M. J. **2**: 566, 1924.
2. Berkeley, C., and Bonney, V.: Textbook of Gynecological Surgery, ed. 4, New York, 1943, Paul B. Hoeber, Inc., p. 535.
3. Bonney, V.: J. Obst. & Gynec. Brit. Emp. **30**: 358, 1923.
4. Salmon, U. J., Walter, R. I., and Geist, S. H.: Am. J. Obst. & Gynec. **42**: 845, 1941.
5. Kennedy, W. T.: Am. J. Obst. & Gynec. **33**: 19, 1937.
6. Kennedy, W. T.: Am. J. Obst. & Gynec. **34**: 576, 1937.
7. Kennedy, W. T.: Am. J. Obst. & Gynec. **41**: 16, 1941.
8. Young, H. H., and Wesson, M. B.: Arch. Surg. **3**: 1, 1921.
9. Young, H. H., and Macht, D.: J. Pharmacol. & Exper. Therap. **22**: 329, 1923.
10. MacAlpine, J. B.: Proc. Roy. Soc. Med. **28**: 39, 1934.
11. Taylor, H. C., and Watt, C. H.: Surg., Gynec. & Obst. **24**: 296, 1917.
12. Kelly, H. A.: Urol. & Cutan. Rev. **17**: 291, 1913.
13. Johnson, H. W.: Surg., Gynec. & Obst. **53**: 97, 1931.
14. Young, E. L.: J. A. M. A. **79**: 1753, 1922.
15. Berkow, S. G.: Am. J. Obst. & Gynec. **41**: 1051, 1941.
16. Counseller, V. S.: Am. J. Obst. & Gynec. **45**: 479, 1943.
17. Kelly, H. A., and Dumm, W. M.: Surg., Gynec. & Obst. **18**: 444, 1914.
18. Furniss, H. D.: Am. J. Obst. & Gynec. **8**: 195, 1924.
19. Davies, J. W.: J. Urol. **48**: 536, 1642.
20. Goebell, R.: Ztschr. f. gynäk. Urol. **2**: 187, 1910.
21. Frangenheim, P.: Verhandl. d. deutsch. Gesellsch. f. Chir. **43**: 149, 1914.
22. Stoeckel, W.: Zentralbl. f. Gynäk. **41**: 11, 1917.
23. Giordano, D.: Assoc. franc. de Chirurg., Congr. de Chir., Paris, **20**: 506, 1907.
24. Squier, J. B.: Med. Rec. **79**: 868, 1911.
25. Taussig, F. J.: Am. J. Obst. **77**: 881, 1918.
26. Thompson, R.: Brit. J. Child. Dis. **20**: 146, 1923.
27. Miller, U.: J. A. M. A. **98**: 628, 1932.
28. Martius, H.: Chirurg. **1**: 769, 1929.
29. Price, P. B.: Arch. Surg. **28**: 1043, 1933.
30. Aldridge, A. H.: Am. J. Obst. & Gynec. **44**: 398, 1942.
31. Studdiford, W. E.: Am. J. Obst. & Gynec. **47**: 764, 1944.
32. Meigs, J. V.: Am. J. Obst. & Gynec. **47**: 774, 1944.

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TREATMENT OF HYPOOVARIANISM BY THE SEQUENTIAL AND CYCLIC ADMINISTRATION OF EQUINE AND CHORIONIC GONADOTROPINS—SO-CALLED ONE-TWO CYCLIC GONADOTROPIC THERAPY

Summary of Five Years' Results*

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THE first series of so-called one-two cyclic gonadotropic therapy was administered, during the latter part of October and the first part of November of 1939, to a patient with ovarian sterility, who became pregnant during the treatment. Details of this therapeutic schedule and the history of this patient were reported by one of us (E. C. H.) about the middle of November, 1939, at the annual meeting of the Southern Medical Association in Memphis, Tennessee. At this time, it was stated that the sequential and cyclic employment of equine and chorionic gonadotropins warranted further and more intensive study. Subsequently, our group gave reports upon results of this therapeutic

*This study was aided by grants to one of us (E.C.H.) as follows: From the Research Council of Duke University; from Ayerst, McKenna & Harrison, Ltd., Montreal, Canada; from Schering Corporation, Bloomfield, N. J.; from The Upjohn Company, Kalamazoo, Mich.; and from the National Committee on Maternal Health, New York, N. Y. Preparations of equine gonadotropin included Anteron (Schering Corporation) and Gonadogen (Upjohn Company); those of chorionic gonadotropin included APL (Ayerst, McKenna & Harrison) and chorionic gonadotropin (Upjohn Company).

schedule in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY of October, 1940,[1] and of March, 1941.[2] Although there have been numerous additional references to this method of treatment in reports by our group, there has been no over-all summary of results since September, 1941.[3] Accordingly, this communication brings up to date our results.

Our clinical studies with gonadotropins began in 1930. In 1932[4] and 1933[5] reports upon the studies of ovaries of women treated preoperatively with chorionic gonadotropin indicated the nonoccurrence of follicle stimulation, ovulation, or corpus luteum elaboration. Similar observations upon larger groups of patients later were reported.[6, 7] Clinical applications of gonadotropic therapy had yielded scanty evidence of success as late as 1939.[8]

The studies of Davis and Koff in 1938[9] of ovarian responses of women treated preoperatively with equine gonadotropin demonstrated the follicle-stimulating activity of this gonadotropin and engendered hopes of its effective application to the therapy of hypoovarianism. To permit effective therapy of hypofunctioning ovaries, a gonadotropin should evoke, in sequence, follicle stimulation, ovulation, and corpus luteum development, and these phenomena should be of physiologic order compatible with fertility and conception. Save for an occasional enthusiastic report, the consensus soon was manifest that equine gonadotropin was failing to warrant earlier therapeutic hopes.

Our group[10] showed that the cyclic administration of equine gonadotropin, in amounts judged to be adequate, during the follicular phase of the cycle—that is, from the fifth to the fourteenth days of the cycle—failed to result in progestational bleeding (as judged by endometrial biopsy studies) or in pregnancy in women who bled from interval or estrogenic endometriums, in many of whom ovarian sterility constituted a major problem.

On the other hand, we showed[3] that, when a similar group of women (with regard to ovarian status and number) was treated with the same equine gonadotropin but, in addition, was given injections of chorionic gonadotropin from the fifteenth through the twenty-fourth days of their cycles, there occurred a substantial number of progestational endometriums and a number of pregnancies. This therapeutic schedule was named one-two cyclic gonadotropic therapy.

This present communication will show that our early impressions of the effectiveness of this therapy have not been altered significantly by the passage of time or by the accumulation of more data.

Selection of Patients

A total of 116 patients with hypofunctioning ovaries was studied.

The patients fell into four clinical categories: (1) those with deficient sexual maturation whose menarches had not occurred, seven patients; (2) those with infrequent and/or scanty bleeding, fourteen patients; (3) those with prolonged and/or excessive bleeding, thirty-one patients; and (4) those with ovarian sterility, sixty-four patients.

These groups embraced the thirty-one patients whose responses were reported in September, 1941.[3] The records of these patients were restudied and re-evaluated.

1. *Patients With Deficient Sexual Maturation Whose Menarches Had Not Occurred.*—All possessed striking hypoestrogenism. In none was a definite diagnosis of hypopituitarism made. Accordingly, the likelihood of an intrinsically ovarian etiology existed in all. The endocrine state of these patients was not relatable to organic or constitutional disease. Hypothyroidism, as an etiological factor, was eliminated by clinical studies, basal metabolic rates and by preliminary treatment with desiccated thyroid gland of those patients in whom there was some evidence of hypothyroidism.

2. *Patients With Infrequent and/or Scanty Bleeding.*—Upon the basis of endometrial biopsies secured at the onsets of episodes of uterine bleeding, all of these patients were

judged to have anovulatory ovarian failure—that is, they bled from interval or estrogenic endometriums. There was no evidence of hypoestrogenism.

No more definite statements of the etiology of the ovarian failure for this group of patients were possible than for the first group.

3. *Patients With Prolonged and/or Excessive Bleeding.*—In common with the patients of the second group, these patients were characterized by anovulatory ovarian failure without hypoestrogenism—that is, all bled from estrogenic or interval endometriums.

Similar to the patients of the first and second groups, no definite diagnoses of the etiology of the ovarian failure were possible; however, constitutional and organic gynecologic factors were excluded.

4. *Patients With Ovarian Sterility.*—This group of patients comprised two subgroups: (a) Patients whose bleeding was associated with interval or estrogenic endometriums, that is, who had anovulatory failure, fourteen in number; and (b) patients whose bleeding occurred from immature progestational endometriums, fifty in number.

We assumed that bleeding from immature progestational endometriums by patients of the second subgroup was significant of endocrine deficiency since no other demonstrable causes of sterility were found in careful diagnostic surveys of these wives and their husbands. We considered two likely mechanisms: (1) ovulations might have occurred and, yet, the immature progestational endometriums might have prevented nidation of any fertilized ova, that is, the existence of hypoprogestinism without anovulatory ovarian failure; and (2) ovulations might not have occurred and, instead, ova were imprisoned in follicles the granulosa of which subsequently became luteinized providing low progestin stimulation of the endometrium, that is, the existence of anovulatory ovarian failure and hypoprogestinism. Acceptance of the latter of these two mechanisms justified the application of one-two cyclic gonadotropic therapy.

No more definite causes for the two grades of ovarian failure of this group of patients were ascribable than for that of the patients of the third group.

All of the patients of the fourth group experienced cyclic and essentially normal bleeding with regard to duration and amount. Therefore, they stand in striking contrast to the patients of the second and third groups.

Method of Study

The clinical studies of all of the patients embraced endocrine and gynecologic surveys, determinations of basal metabolic rates, and roentgenograms of the sella turcica. Roentgenologic estimations of osseous age were made in those patients with deficient sexual maturation and those 20 years or less of age. Endometrial biopsies were done at the onset of episodes of bleeding, prior to, during, and frequently after therapy. Because of the hypoestrogenism of the patients of the first group, initial biopsies were omitted. At least two consecutive episodes of bleeding were biopsied, if possible, prior to treatment of the patients of the second, third, and fourth groups. This seemed advisable lest chance variations might be classed as ovarian habits of a patient.

All biopsy material, after fixation, mounting, and staining, was studied and classified by one of us (E.C.H.). This practice has been followed in previous studies and, thereby, has permitted a uniformity and continuity of interpretation of endometrial responses.

Special methods of study and of handling of the patients of the four groups are detailed.

1. *Patients With Deficient Sexual Maturation Whose Menarches Had Not Occurred.*—Urinary levels of gonadotropins and 17-ketosteroids were established in some of these patients. (These data will be reported in subsequent communications.) Studies of vaginal smears, stained by Mack's iodine vapor method,[11] were made prior to and during therapy; the results were in essential agreement with the other data to be reported.

Cyclic estrogen therapy was given to produce sexual maturation and to initiate withdrawal bleeding. Cyclic estrogen-progesterone therapy then followed, and endometrial biopsies were taken at the onsets of subsequent bleeding episodes. When an endometrial biopsy showed a progestational endometrium, treatment was discontinued and, subsequently, when bleeding followed twenty-eight to thirty days of no treatment or even when bleeding did not recur after this length of time, an endometrial biopsy was taken as a salvage test. The purpose of the salvage test was to exclude the recovery of normal ovarian function during the antecedent cyclic steroid therapy. When a progestational endometrium was found on salvage test, the patient was not given gonadotropic therapy.

The purpose of the cyclic estrogen-progesterone therapy is to prove the endometrium capable of responding to progestin. This is essential to the use of the endometrium as an indicator of the effectiveness of gonadotropic therapy. If an endometrium is incapable of responding to progestin therapy, it will fail to respond to any progestin which is caused to be elaborated by the ovaries by gonadotropic therapy.

Following a negative salvage test, one-two cyclic gonadotropic therapy was given and endometrial biopsies were taken, either at the onset of bleeding following this therapy or within seven days after the conclusion of therapy if no bleeding occurred. A positive response was the finding of a progestational endometrium.

Previous clinical experience had not indicated that we should expect regulation of bleeding from gonadotropic therapy. The present studies agreed.

2. *Patients With Infrequent and/or Scanty Bleeding.*—The method of study of these patients was essentially that of the first group. These patients did not require cyclic estrogen therapy for sexual maturation and, accordingly, were given only cyclic estrogen-progesterone therapy. This served both to regulate their bleeding and as a test of endometrial receptivity. The salvage test after this therapy was done and gonadotropic therapy was evaluated as in patients of the first group.

3. *Patients With Prolonged and/or Excessive Uterine Bleeding.*—The majority of these patients was seen during episodes of prolonged and/or excessive uterine bleeding. These patients required, as the first measure, control of the excessive and/or prolonged flowing. This was accomplished generally by the hemostatic use of estrogen. Once hemostasis was obtained, cyclic estrogen therapy was given to regulate the cycle and to secure withdrawal bleeding of essentially normal duration and amount.

Endometrial evaluations of these patients, which were used as base lines for gonadotropic therapy, were made after cycle regulation had been secured and after steroid therapy was discontinued.

Cyclic estrogen-progesterone therapy was used as a test for endometrial responsiveness and a salvage test was done as in the patients of the first and second groups. Patients who gave a negative salvage test were treated with one-two cyclic gonadotropic therapy and the results of this therapy were evaluated as previously described.

4a. *Patients With Ovarian Sterility Characterized With Estrogenic Bleeding.*—These patients were handled identically with those of the second and third groups as to a test of endometrial receptivity with cyclic estrogen-progesterone therapy, salvage test, and one-two cyclic gonadotropic therapy.

4b. *Patients With Presumed Sterility and Immature Progestational Bleeding.*—These patients did not require a test of endometrial receptivity since they bled from progestational endometriums. A salvage test was unnecessary for the same reason. One-two cyclic gonadotropic therapy was given and its results were tested as in the other groups.

In both sterility groups the occurrence of pregnancy during therapy was regarded as a positive response.

Therapeutic Schedules

The therapeutic schedules used in these studies are summarized.

Hemostasis.—The average daily dosage of estrogen employed for hemostasis is represented by 6 mg. of diethylstilbestrol or its equivalent in estrone sulfate. Not all patients were treated with oral estrogens during the earlier years of the study. A comparable amount of estrogen by injection was used. After hemostasis was obtained, estrogen therapy at the same dosage level was continued daily for another twenty days.

Cyclic Estrogen Therapy.—Cyclic estrogen therapy was begun on the third to fifth day of the cycle and continued for twenty days, when it was withdrawn, or earlier if bleeding occurred. It was resumed on the third to the fifth day of the cycle. This therapy was usually kept up two or three months.

The usual daily dosage is represented by 3 mg. of diethylstilbestrol or its equivalent in estrone sulfate. The majority of patients were treated orally; however, in earlier years, some received injections.

Cyclic Estrogen-Progesterone Therapy.—This therapy was started on the fifth day of the cycle. Estrogen was given orally and in daily dosages represented by 3 mg. of diethylstilbestrol, or the equivalent in estrone sulfate, for twenty days. During the last ten days of this treatment, the patient received orally and daily 60 mg. of anhydrohydroxy-progesterone. Not all patients received oral therapy. Some received similar amounts of estrogen and progesterone by injection in the earlier years of the study.

One-Two Cyclic Gonadotropic Therapy.—Prior to initiating one-two cyclic gonadotropic therapy, all patients were skin tested with the equine gonadotropin preparation to ascertain possible allergy. Skin tests were repeated before each projected series of therapy. Patients with definite allergy were not treated.

Gonadotropins were given intramuscularly and daily. Therapy was initiated on the fifth day of the cycle. From the fifth through the fourteenth days of the cycle, patients received intramuscularly and daily 400 international units of equine gonadotropin. From the fifteenth through the twenty-fourth days of the cycle, patients received intramuscularly and daily 500 international units of chorionic gonadotropin. When bleeding occurred before treatment was completed, injections were discontinued.

As a rule, and out of respect for possible antibody or antihormonal phenomena, series of one-two cyclic gonadotropic therapy were not given in sequence but, instead, several months were allowed to elapse between any two series of therapy.

Clinical Data and Results

1. *Patients With Deficient Sexual Maturation Whose Menarches Had Not Occurred.*—The ages of these seven patients ranged from 16 to 26 years. The average age was 19.5 years.

These seven patients received eleven series of one-two cyclic gonadotropic therapy. The results of ten of these eleven series of therapy were sampled by endometrial biopsies. Ninety per cent of the endometrial biopsies, or nine biopsies, yielded estrogenic endometriums: eight hypoestrogenic and one quite adequately proliferated. Ten per cent, or one biopsy, showed an immature progestational endometrium.

The patient from whom the immature progestational endometrium was obtained gave this response on the third series of gonadotropic therapy. The other two series of therapy given this patient had yielded hypoestrogenic endometriums.

Five of the seven patients bled following gonadotropic therapy. One of the five patients received three series of gonadotropic therapy and bled after one series but did not bleed after the other two series. None of the patients had subsequent bleeding except when they were given cyclic steroid therapy.

2. *Patients With Infrequent and/or Scanty Uterine Bleeding.*—The ages of these fourteen patients ranged from 17 to 35 years, thus placing all of them in the late adolescent or reproductive epochs. The average age was 25 years.

The menarcheal ages of these patients ranged from 10 to 17 years with an average of 13.3 years.

Seven were single and seven were married. Of the seven married patients, four were nulliparous and the others had had, respectively, one abortion, one term delivery, and two term deliveries.

The character of their bleeding histories varied. Seven reported last episodes of bleeding ranging from four years to six months. Five patients had intervals ranging from three to six months. Two patients had intervals which ranged from two to three months in length. The bleeding in many of these patients was scanty in amount and short in duration.

Twelve of the patients bled from well-developed estrogenic endometriums and two bled from hypoestrogenic endometriums.

The fourteen patients received twenty-two series of one-two cyclic gonadotropic therapy. Seventeen of these series of therapy which were given thirteen of the fourteen patients were sampled by endometrial biopsies. Four patients (30.8 per cent) yielded progestational endometriums following treatment: three patients, immature progestational endometriums, and one patient, a full-blown progestational endometrium. The other nine patients yielded estrogenic endometriums: six normal estrogenic endometriums and three hypoestrogenic endometriums.

In none of the patients were the duration and amount of bleeding affected or the irregularity of the cycle improved.

One of the patients who gave a positive response had a follow-up biopsy at the onset of bleeding one month following discontinuation of treatment; this biopsy indicated a full-blown progestational endometrium.

3. *Patients With Prolonged and/or Excessive Uterine Bleeding.*—The ages of these thirty-one patients ranged from 14 to 31 years, an average age of 23.5 years. Accordingly, all of these patients were in the adolescent or the early reproductive epochs.

Menarcheal ages of these patients varied from 11 to 16 years, an average age of 13 years.

Eighteen of these patients were single and thirteen were married. Of the thirteen married patients, eight were nulliparous, three had had a pregnancy which resulted in a term delivery, one had had four abortions and a term pregnancy, and one had had an abortion.

The character of the bleeding history of these patients varied. When first seen, twenty-two patients had had continuous bleeding ranging from one month to four years. Nine patients were having various grades of prolonged and/or profuse bleeding, six being cyclic and three being infrequent. The severity of the hemorrhage of these patients is indicated by their hemoglobin readings which ranged from 10 to 100 per cent with an average of 62 per cent. Sixteen patients had hemoglobins less than 60 per cent.

All patients, prior to therapy, bled from estrogenic endometriums.

A total of fifty-three series of one-two cyclic gonadotropic therapy was given to the thirty-one patients. Fourteen, or 45.2 per cent, yielded progestational endometriums. One patient gave a positive response during each of two series of treatment. There were six full-blown progestational and nine immature progestational endometriums encountered during therapy. A total of fifteen series of therapy, therefore, terminated in progestational bleeding, whereas thirty-two series of therapy terminated in estrogenic bleeding; the results of six series were not sampled by biopsy.

Follow-up biopsies, which were done usually at the first episodes of bleeding which terminated no treatment cycles, subsequent to gonadotropic therapy, were done twenty-three times in nineteen patients. Nine of the nineteen patients yielded progestational endometriums: full-blown progestational endometriums in two patients and immature progestational endometriums in seven patients. Seven of these nine follow-up progestational responses occurred in patients who had had progestational endometriums during gonadotropic therapy, whereas two occurred in patients who had yielded estrogenic endometriums during therapy.

Accordingly, 45.2 per cent of the patients yielded progestational responses concurrent with gonadotropic therapy, whereas 47.4 per cent of the patients, followed up after discontinuation of therapy, yielded progestational responses one month or more after the treatment ended. When several follow-up biopsies were done after therapy, it was found generally that the progestational response gave way to an estrogenic response on the second biopsy.

4a. *Patients With Ovarian Sterility Associated With Estrogenic Bleeding.*—The ages of these fourteen patients ranged from 24 to 35 years. The average age was 29 years.

Menarcheal ages of these patients ranged from 11 to 14 years. The average age was 12.6 years.

Ten of these patients were nulliparous. Two had had a term delivery, and two an abortion.

The duration of the sterility of these patients ranged from one to ten years. The average duration was 3.4 years.

All pretreatment biopsies on these patients yielded normally proliferated estrogenic endometriums.

These fourteen patients received twenty-one series of one-two cyclic gonadotropic therapy, an average of 1.5 series per patient.

The endometrial responses of seven of these patients were not sampled by biopsy; however, two of these patients became pregnant during the first series of treatment and one during the second series of treatment. The occurrence of pregnancy in these three patients, therefore, is assumed to indicate positive ovarian responses.

The endometrial responses were sampled by biopsy in the other seven patients. Four of these patients yielded progestational responses, three yielding immature progestational endometriums and the other a decidua-like endometrium. The subsequent course of this last patient indicated that implantational bleeding had occasioned biopsy rather than menstrual bleeding. The pregnancy of this patient, however, progressed normally.

Accordingly, gonadotropic therapy of these fourteen patients resulted in four pregnancies, whereas three other patients gave progestational responses. Thus, the incidence of positive response was 50 per cent and the incidence of pregnancy was 28.6 per cent. Two of the pregnancies resulted in term deliveries of normal children, one is nearing term, and the other is yet in an early stage.

4a. *Patients With Ovarian Sterility Associated With Bleeding From Immature Progestational Endometriums.*—The ages of these fifty patients ranged from 21 to 41 years; twenty-four patients were between 21 and 29 years of age; twenty-three were between 30 and 39 years of age; and three patients were between 40 and 41 years of age.

Menarcheal ages of these patients ranged from 11 to 17 years, the average being 12.9 years.

Thirty-seven of these patients were nulliparous. Five had had a term delivery, five an abortion, two had had two abortions and one four abortions.

The duration of the sterility of these patients ranged from one to ten years, an average sterility of 3.08 years.

A total of ninety-one pretreatment biopsies was done upon the fifty patients, with an incidence of 1.82 biopsies per patient. Distribution of the biopsy findings was: inadequate tissue for diagnosis, three; estrogenic endometriums, five; full-blown progestational endometriums, nine; and immature progestational endometriums, seventy-four. All of the patients, however, presented immature progestational endometriums as a predominant bleeding pattern.

These fifty patients received ninety-six series of one-two cyclic gonadotropic therapy, an average of 1.96 series per patient.

No endometrial biopsies were done during eighty-one cycles or after 84.3 per cent of the series of treatment. The criterion for responses in these was the occurrence of pregnancy.

Of the fifteen cycles of therapy, the results of which were sampled by biopsy, eight cycles terminated in bleeding from immature progestational endometriums, six cycles in bleeding from full-blown progestational endometriums, and one cycle could not be evaluated because of insufficient tissue. These fifteen cycles were distributed among fourteen of the fifty patients. Of these fourteen patients, three became pregnant. All of these patients yielded full-blown progestational endometriums following therapy. One pregnancy occurred the month following a second series of treatment. The second pregnancy occurred during a second series of therapy. The third pregnancy occurred during the first series of treatment and its associated implantational bleeding led to inadvertent biopsy.

Of the thirty-six patients whose responses to therapy were judged only by the occurrence of pregnancy, six became pregnant. Four of these pregnancies occurred during the first series of therapy. Two occurred during the second series of therapy. Accordingly, the fifty patients yielded a total of nine pregnancies, or 18 per cent of the patients treated became pregnant. A total of thirteen series of therapy, or an average of 1.44 series per patient, was given the nine patients.

Four of the nine pregnancies resulted in term deliveries of healthy children; one resulted in a stillbirth at five months, the cause being a true knot in the cord; and four resulted in abortions at about the third month.

Discussion

Those patients with anovulatory ovarian failure, characterized by diverse types of estrogenic bleeding, supply our most clear-cut data of the effectiveness of one-two cyclic gonadotropic therapy. They are included in the second and third groups and in the first subgroup of the fourth group, i.e., those with infrequent and/or scanty bleeding, those with prolonged and/or excessive bleeding and those with ovarian sterility characterized by estrogenic bleeding.

The results which are reported in this communication warrant comparison with those of our report of September, 1941:

Patients With Infrequent and/or Scanty Bleeding.—Present report: Positive responses in four of thirteen patients, or 30.8 per cent. *September, 1941, report:* Positive responses in five of eight patients, or 62.8 per cent.

Patients With Prolonged and/or Excessive Bleeding.—Present report: Positive responses in fifteen of thirty-one patients, or 48.5 per cent. *September, 1941, report:* Positive responses in seven of eighteen patients, or 38.9 per cent.

Patients With Ovarian Sterility Characterized by Estrogenic Bleeding.—Present report: Positive responses in seven of fourteen patients (including four pregnancies), or 50 per cent. *September, 1941, report:* Positive responses in three of three patients (including two pregnancies), or 100 per cent.

Total Patients of the Three Groups.—Present report: Positive responses in twenty-six of fifty-eight patients, or 44.8 per cent. *September, 1941, report:* Positive responses in fifteen of twenty-nine patients, or 51.7 per cent.

These data indicate, therefore, that an expansion of the number of patients treated with one-two cyclic gonadotropic therapy has not altered markedly our total percentage salvage from that reported in September, 1941. In our analysis of the total data which comprise this report we have been more critical, perhaps, than in that of the previous report. This may account in part for some differences in final figures.

The present report differs from the previous one by presenting data upon a group of fifty women with ovarian sterility which is presumed to be related to bleeding from immature progestational endometriums. The fact that nine of these fifty women became pregnant during one-two cyclic gonadotropic therapy appears to justify our diagnostic assumption, certainly in these nine women. The records of the other forty-one patients of this group who did not become pregnant under one-two cyclic gonadotropic therapy are interesting. Only five of these ultimately became pregnant. Four of the pregnancies occurred three months after the last series of one-two cyclic gonadotropic therapy and one, six months after the last series of treatment. It is considered unlikely, therefore, that the treatment which these patients received resulted in the pregnancies. We cannot, and have not, related these pregnancies to therapy. It is obvious that our diagnostic ability in this group is not good since only 18 per cent of the patients we treated upon our theory of endocrine sterility actually became pregnant. We believe, however, that to salvage pregnancies in 18 per cent of a group of patients, which previously had been accepted by us as having essentially normal ovarian function, represents a distinct addition to the total salvage of pregnancies from couples of low fertility.

When we consider those patients with ovarian sterility in association with estrogenic bleeding, we find that, of the seven patients who did not yield positive responses to one-two cyclic gonadotropic therapy, none became pregnant. Five of the seven patients who did respond positively to therapy became pregnant. Four of these pregnancies were relatable directly to treatment. Therefore, the seven patients who responded positively yielded the only pregnancies in this group, that is, a total of five pregnancies.

When the two groups of patients with ovarian sterility are combined, that is, those who bled from immature progestational endometriums and those who bled from estrogenic endometriums, we find that a total of thirteen pregnancies in sixty-four patients was attributable to one-two cyclic gonadotropic therapy, an incidence of pregnancies of 20.3 per cent in the patients with ovarian sterility.

Results of treatment of the group of patients with deficient sexual maturation associated with nonoccurrence of menarche were quite poor and were in line with pretreatment expectations. It was thought that these patients probably represented a group in which intrinsic ovarian inadequacy rendered stimulational therapy quite unlikely to be successful. All forms of endocrine therapy apparently fail to effect full salvage in this group.

A statement about the allergic propensities of preparations of equine gonadotropin is in order. The practice of doing skin tests before administration of each series of this therapy is justified; however, only one patient to whom we have attempted to give equine gonadotropin proved so allergic that it was impossible to carry on treatment. This patient, obviously, is not included in this series. She had a long history of asthma and allergy. The patient gave a very positive skin test and, because of this and her history, no attempt was made to treat her.

All of the severe reactions which have been described by other workers have followed the intravenous administration of equine gonadotropin.[12] All of our treatments with this gonadotropin have been given intramuscularly.

Finally, some statement is indicated regarding the mechanism of action of one-two cyclic gonadotropic therapy. This may be an expression of a synergism between equine and chorionic gonadotropins. When full follicular maturation has been secured from ten days of equine gonadotropin therapy, ovulation and normal corpus luteum development and function follow the administration of chorionic gonadotropin. Our experience with pregnancies, which have occurred during this therapy, leads us to believe that ovulation occurs within twenty-four to forty-eight hours after the initiation of chorionic gonadotropin fraction of the treatment schedule. The one-two gonadotropic system of therapy may be viewed as duplicating the normal biphasic cycle of pituitary gonadotropic activity.

The dosage schedules which we have employed were selected rather arbitrarily. There is no reason, however, to believe the dosages are too large, since in no patient have we encountered undue ovarian enlargement or cystic change. Larger doses are being investigated and the results of their use will be reported later. They may enhance our salvage rates.

Summary and Conclusions

A total of 116 hypoovarian patients, whose ages placed them in the adolescent or reproductive epochs, was treated by the sequential and cyclic administration of equine and chorionic gonadotropins. The following results were obtained:

1. Only one of seven patients with deficient sexual maturation and nonoccurrence of menarche (hypoestrogenism) yielded a progestational endometrium during therapy.

2. Four of thirteen patients, or 30.8 per cent, with infrequent and/or scanty estrogenic uterine bleeding yielded progestational endometriums during therapy.

3. Fifteen of thirty-one patients, or 48.5 per cent, with prolonged and/or excessive estrogenic bleeding yielded progestational endometriums during therapy.

4. Seven of fourteen patients, or 50 per cent, with cyclic estrogenic bleeding and ovarian sterility yielded positive responses, including four pregnancies, during therapy.

5. Nine of fifty patients, or 18 per cent, with cyclic bleeding from immature progestational endometriums became pregnant during therapy.

The following conclusions appear warranted:

1. Patients with hypoestrogenism (as illustrated by those with deficient sexual maturation) respond poorly to this system of gonadotropic therapy.

2. Patients with anovulatory ovarian failure without hypoestrogenism (as illustrated by those with diverse types of estrogenic bleeding) respond well to this system of therapy: a total of 44.8 per cent yielded progestational endometriums.

3. A small percentage (18 per cent) of sterile women, whose bleeding from immature progestational endometriums constitutes the only significant finding upon their surveys or those of their husbands, become pregnant when treated with one-two cyclic gonadotropic therapy.

References

1. Hamblen, E. C.: Am. J. Obst. & Gynec. 40: 615, 1940.
2. Hamblen, E. C.: Am. J. Obst. & Gynec. 41: 495, 1941.
3. Hamblen, E. C., Cuyler, W. K., Wilson, J. A., and Pullen, R. L.: J. Clin. Endocrinol. 1: 749, 1941.
4. Hamblen, E. C.: ref. by J. P. Pratt in Sex and Internal Secretions, ed. 1, Baltimore, 1932, Williams & Wilkins Co., pp. 900-901.
5. Hamblen, E. C.: Virginia M. Monthly 60: 286, 1933.
6. Hamblen, E. C., and Ross, R. A.: Am. J. Obst. & Gynec. 31: 14, 1936.
7. Hamblen, E. C., and Ross, R. A.: Endocrinology 21: 722, 1937.
8. Hamblen, E. C.: Endocrinology 24: 848, 1939.
9. Davis, M. E., and Koff, A. K.: Am. J. Obst. & Gynec. 36: 183, 1938.
10. Hamblen, E. C., Cuyler, W. K., Wilson, J. A., and Pullen, R. L.: J. Clin. Endocrinol. 1: 742, 1941.
11. Mack, H. C.: J. Clin. Endocrinol. 3: 169, 1943.
12. Bickers, W.: J. Clin. Endocrinol. 1: 852, 1941.

(A related paper will be included in the next issue.)

THE EFFECT OF RESPIRATORY STIMULANTS IN THE NEWBORN INFANT

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AMONG the methods commonly employed for the resuscitation of asphyxiated infants at the time of birth, the use of drugs which stimulate respiration has been extensively tried. Clinical trial has left considerable uncertainty, however, both as to their effectiveness in overcoming respiratory depression and as to the margin of safety from the danger of overdosage.

Various considerations have prompted the use in asphyxia neonatorum of drugs such as alpha-lobeline, coramine, caffeine, metrazol, and cyanide. The recognition in recent years of the importance of reflex control of respiration involving the carotid body mechanism has increased interest in the possibility of affecting peripheral chemoreceptors rather than centering attention merely upon the hydrogen ion concentration or the carbon dioxide tension of the blood. There is evidence that the carotid body receptors are more resistant than the cells of the center to depression by narcotics, anoxia, and excessive CO_2 (Comroe and Schmidt, 1938[1]). Consequently, extensive trial of pharmacologic agents which influence the nervous mechanism of respiration has been made (Marshall and Rosenfeld, 1937[2]). One of the major problems to be attacked from this new approach has been asphyxia in the newborn infant. Additional impetus was afforded by the reports of favorable response to analeptic agents when employed to combat overdosage of barbiturates in the adult (Werner and Tatum, 1939[3]). Great importance has been attached at times to the prompt initiation of the first gasp after birth and the efficiency of agents such as alpha-lobeline in accomplishing this result (Wilson, Torrey, and Johnson, 1938;[4] Russ and Strong, 1941[5]). Metrazol, coramine, and alpha-lobeline have been used even before birth when signs of intrauterine asphyxia of the fetus appeared, the drugs being injected into the mother. By administration before birth it has been claimed that these drugs may aid in the prevention of asphyxia by effects upon the fetal circulation (Stuppy, 1940;[6] Dörr, 1938;[7] Nevinny, 1937[12]).

Under clinical conditions the role of stimulant drugs in the resuscitation of newborn infants has been difficult to evaluate because of the numerous complications which are associated with delivery, such as anesthesia, anoxemia, and mechanical trauma. In the case of failure of resuscitation, the question arises as to whether or not adequate dosage was administered, or, on the other hand, whether the margin of safety was exceeded and the toxic effect of these powerful drugs was exerted. In the event of survival it has been difficult to demonstrate that these drugs effectively influenced the outcome.

The present investigation is an attempt to determine the effect upon the *normal* newborn infant of various respiratory stimulants, including alpha-lobeline, coramine, metrazol, caffeine, and cyanide. The aim in the present experiments is first, to take into account the peculiarities of the newly born animal in response to these powerful agents; second, to eliminate numerous complicating factors commonly associated with clinical trial.

Method and Material

Newborn rabbits were used in the present experiments. In order to record kymograph tracings of the rate and depth of respiratory movements, the entire body of the animal below the neck was enclosed in a small plethysmograph connected with a recording tambour as previously described (Rosenfeld and Snyder, 1938[8]). The animal was placed on his back in horizontal position with arms and legs fastened to a rigid board. The external jugular vein was readily exposed for injection, and the drugs were administered intravenously by a syringe with graduations of 0.01 c.c. Control injections of Ringer's solution were made throughout. The rate of administration was rapid, the injection being completed within a minute.

After the immediate response to various drugs had been tested in the plethysmograph, the animals were removed and remained under observation in order to detect more remote effects or failure to survive.

The observations are based upon 83 newborn rabbits obtained from 41 litters. In one group consisting of 57 newborn obtained from 26 litters, pentobarbital sodium in dosage of 20 to 30 mg. per kilogram was injected subcutaneously one hour before the respiratory stimulants were tested. After this dosage the general activity of the newborn animals was reduced sufficiently to afford tracings of the respiratory movements which were much less obscured by struggling movements than in a control series in which pentobarbital was not given. Furthermore, since barbiturates are widely used during labor, it is of added interest to observe the responses of the newborn to respiratory stimulants under conditions resembling those of clinical trial. In a second group consisting of 26 newborn of 15 litters, premedication was omitted. All litters were from animals which were mated in the laboratory and hence the age of the offspring was accurately known. Observations were made within twenty-four hours following birth. In addition to the newborn animals, a series of rabbits was studied during the later neonatal period at a time when respiratory responses were well established. In this group there were 21 rabbits obtained from 13 litters ranging in age from about 1 to 4 weeks and varying in weight from 75 to 320 grams.

Observations

Alpha-lobeline.—In newly born rabbits the intravenous injection of alpha-lobeline* was followed by disturbances of respiration, but it was difficult to determine a dosage at which stimulation occurred as indicated by increase in rate and amplitude of respiratory movements. Furthermore, the changes in respiration were brief, usually lasting less than a minute unless the convulsive level of dosage was reached. Thus, in Fig. 1, the respiratory movements were recorded following injection of the same animal with different dosages. Administration of 0.05 mg. of alpha-lobeline failed to increase the rate and amplitude of respiration. However, merely twice this amount, or 0.10 mg., resulted in transient depression of respiratory movements and convulsive seizures. In testing responses at various levels of dosage a single injection of one animal was made in many experiments, rather than repeated injections, and

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TABLE I. RESPONSE OF NEWBORN RABBITS TO RESPIRATORY STIMULANTS

DRUGS	NEWBORN RABBITS (NO.)	LITTERS (NO.)	MINIMAL EFFECTIVE DOSE (MG./KG.)	MINIMAL CONVULSIVE DOSE (MG./KG.)	RATIO OF M. C. D. / M. E. D.	SURVIVAL
α-Lobeline	12	4	2	4	2	?
Coramine	13	8	100	300	3	?
Caffeine	14	6	100	200	2	?
Metrazol	14	4	100	200	2	+
Cyanide	4	4	0.05	0.15	3	+
Premedication: Pentobarbital sodium 20-30 mg./kg. subcutaneously.						

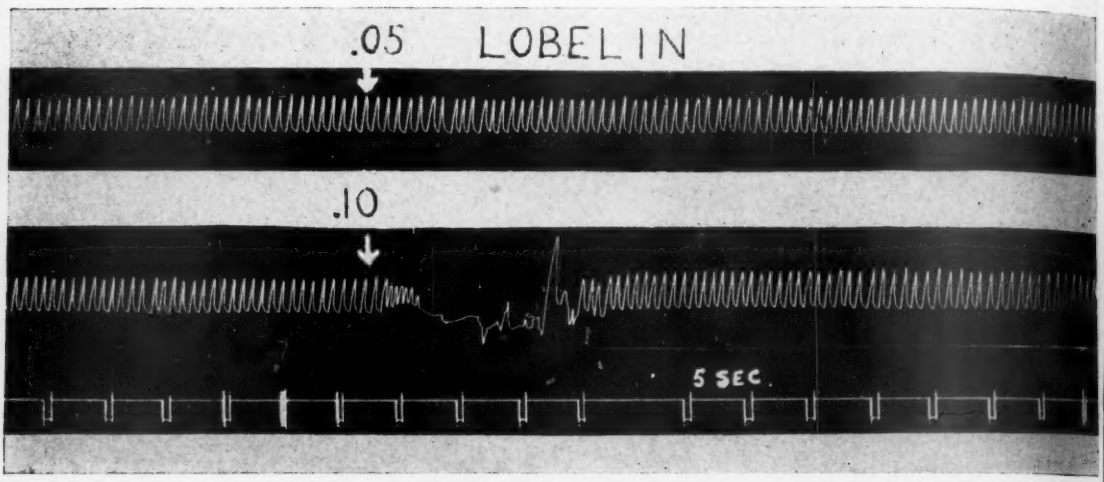

Fig. 1.—Effect of alpha-lobeline upon respiration of a newborn rabbit. Intravenous injection of 0.05 mg., i.e., 1 mg./kg. failed to increase rate or amplitude of respiration; 0.10 mg. in the same animal resulted in depression. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously.

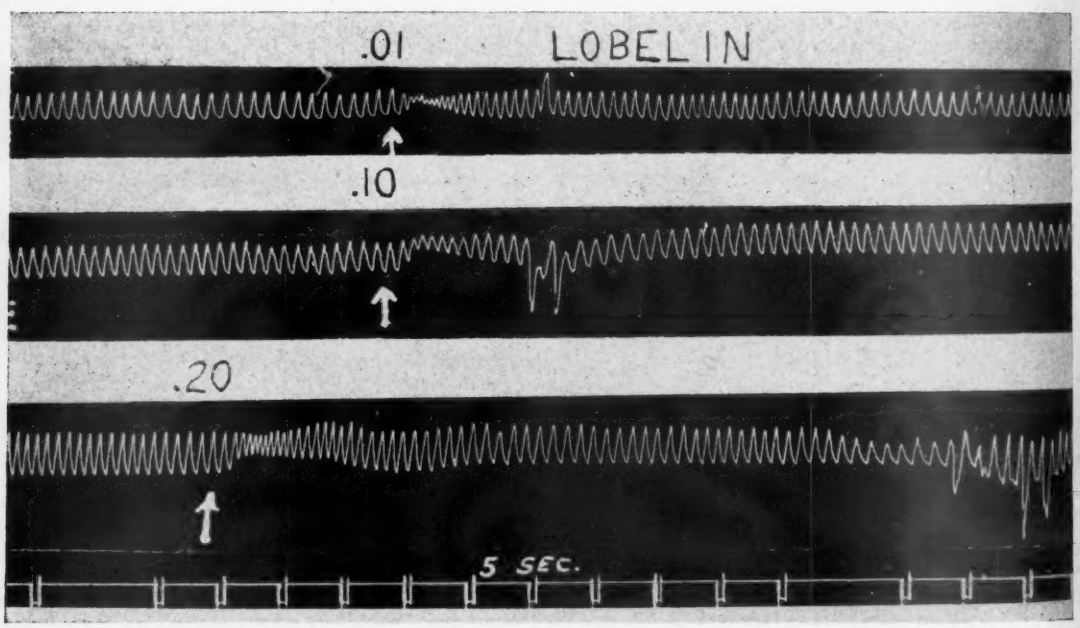

Fig. 2.—Effect of alpha-lobeline upon respiration of three newborn rabbits at different dosage levels: (1) 0.01 mg. i.e., 0.20 mg./kg. intravenously; (2) 0.10 mg., i.e., 2.0 mg./kg. intravenously; (3) 0.20 mg., i.e., 4.0 mg./kg. intravenously. Failure of stimulation. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously.

usually littermates were used. Despite the use of fresh animals, results as illustrated in Fig. 2 show failure to obtain stimulation of respiration after a dosage of 0.01 mg., after 0.10 mg., and finally after 0.20 mg. of alpha-lobeline at which level convulsions occurred. The series included 12 newborn rabbits obtained from 4 litters. (Table I.)

When premedication with pentobarbital sodium was omitted, convulsions were noted following a dose of 0.10 mg., i.e., 2 mg. per kilogram; and irregular respiratory movements but not definite stimulation followed a dose of half this amount. The group included 11 newborn obtained from 6 litters.

Coramine.—Following the injection of 5 mg. of coramine,* respiratory movements showed transient changes lasting less than a minute. As the dosage was increased, the depth of breathing rather than the rate showed some increase (Fig. 3). Convulsions appeared at a dosage level which was about three times the minimal effective amount. The group included 13 newborn obtained from 8 litters.

When pentobarbital sodium was not given, convulsions were observed following a dose of 1 mg., i.e., 20 mg. per kilogram; no definite stimulation of respiration was noted at lower dosage levels. Observations were made on 6 newborn obtained from 4 litters.

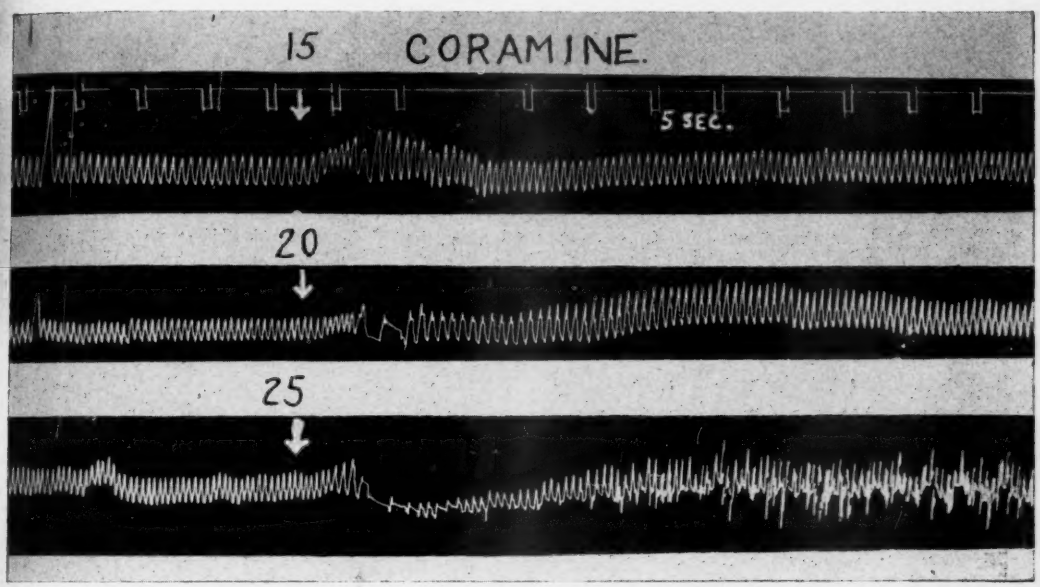

Fig. 3.—Effect of coramine upon respiration of the same newborn rabbit at various dosage levels: (1) 15 mg., i.e., 0.3 Gm./kg. intravenously; (2) 20 mg., i.e., 0.4 Gm./kg. intravenously; (3) 25 mg., i.e., 0.5 Gm./kg. intravenously. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously.

Caffeine.—Following administration of 5 mg. of caffeine sodiobenzoate,† respiratory movements showed an increase in depth but not rate (Fig. 4). The changes disappeared within a period of less than a minute. As the dosage was increased, breathing became deeper but not more rapid. Convulsions were noted at a dosage level which was twice that of the minimal effective amount. Recurrence of deep gasps with definite periodicity was a characteristic effect of caffeine in the entire series. The group included 14 newborn obtained from 6 litters.

In the absence of pentobarbital sodium, convulsions were noted after a dose of 5 mg., i.e., 100 mg. per kilogram, and slight increase in depth of respiration was seen after one-half this dosage. Four newborn from 2 litters were studied.

Metrazol.—The injection of 5 mg., or 100 mg. per kilogram of body weight, of metrazol‡ was followed by an increase in rate and amplitude of respiratory movements which persisted for a period of less than a minute. Administration of twice this amount, namely, 10 mg., resulted in striking convulsive seizures (Fig. 5).

When pentobarbital sodium was omitted, convulsions were noted with doses ranging from 0.5 to 2 mg., or 10 to 40 mg. per kilogram, in a group of 5 newborn from 3 litters.

*Ciba Pharmaceutical Products, Inc.
†Sharp & Dohme, Inc.
‡Bilhuber-Knoll Corporation.

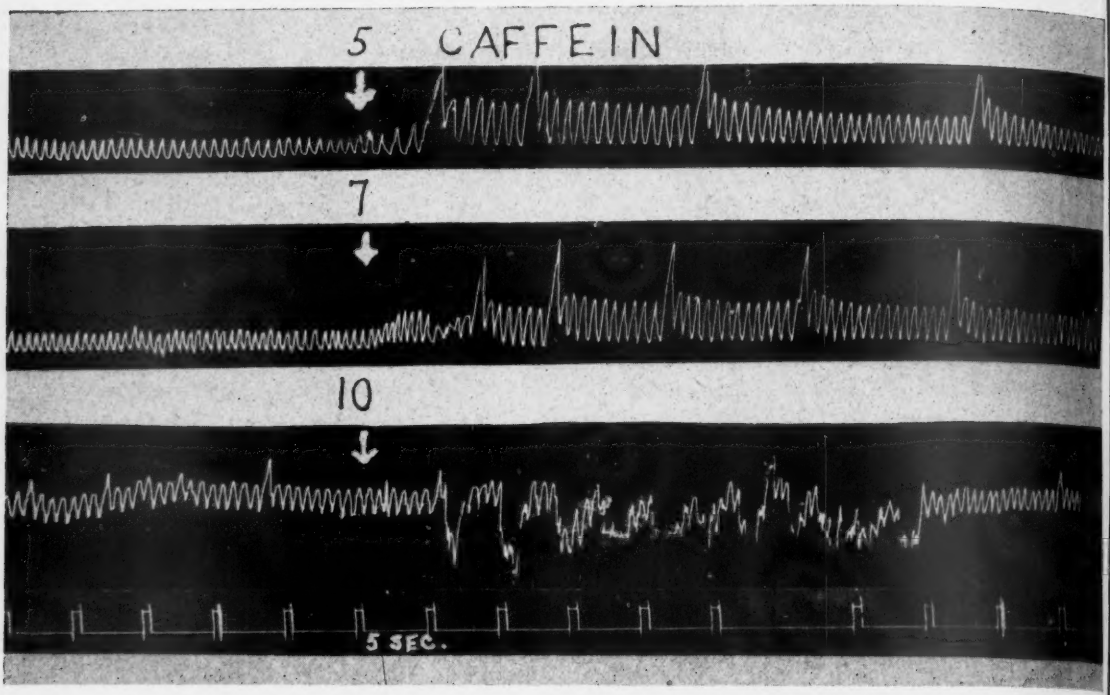

Fig. 4.—Effect of caffeine sodiobenzoate upon respiration of the same newborn rabbit at various dosage levels: (1) 5 mg., i.e., 0.1 Gm./kg. intravenously; (2) 7 mg., i.e., 0.14 Gm./kg. intravenously; (3) 10 mg., i.e., 0.2 Gm./kg. intravenously. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously.

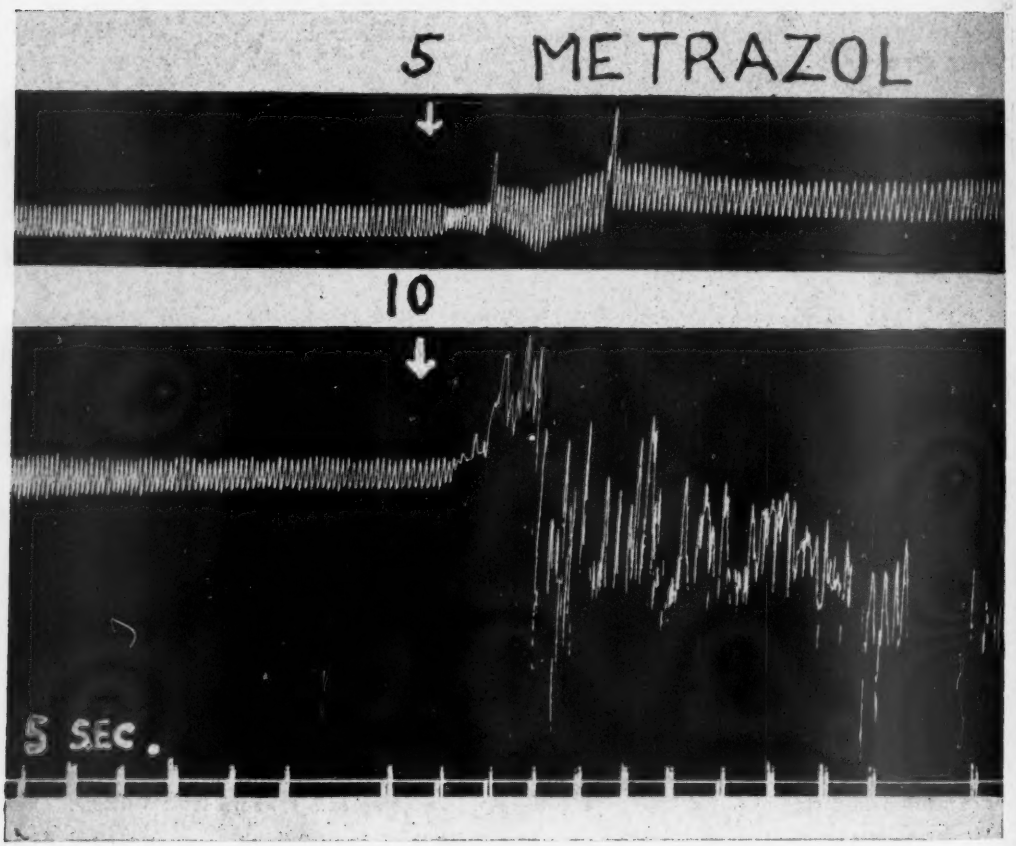

Fig. 5.—Effect of metrazol upon respiration of the same newborn rabbit. Intravenous injection of 5 mg., i.e., 0.1 Gm./kg. gave an increase in rate and amplitude, while twice this amount resulted in convulsive seizures. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously.

Cyanide.—The response to injection of sodium cyanide and pyruvic acid cyanhydrin, with which Dr. Morris Rosenfeld of the Department of Pharmacology of the Johns Hopkins University provided us, was marked by definite stimulation of respiration, both depth and rate being increased. The effect was not prolonged, however, lasting about a minute or less. The margin was not large between the minimal stimulating dose and the depressant or convulsive level. Administration intravenously of 0.0025 mg. sodium cyanide, i.e., 0.05 mg. per kilogram, gave stimulation, while irregular convulsive movements followed a dosage three times as great, or 0.15 mg. per kilogram. Following 0.05 c.c. of 0.016 molar cyanhydrin, stimulation occurred, while twice this amount, or 0.10 c.c., resulted in convulsions (Fig. 6). Observations were made on 4 fetuses obtained from 4 litters.

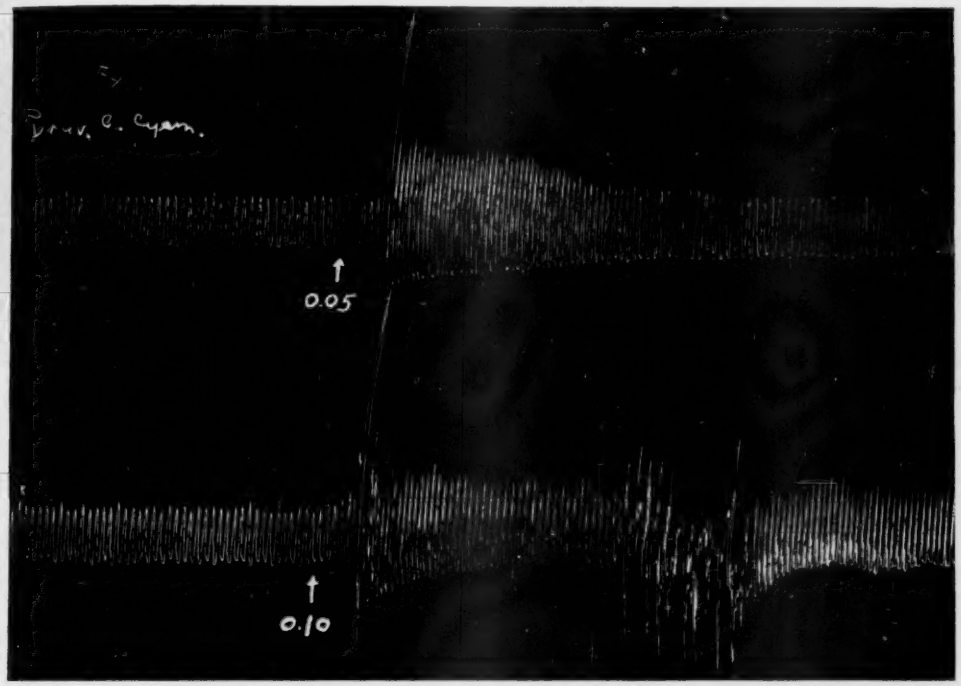

Fig. 6.—Effect of pyruvic acid cyanhydrin upon respiration of the same newborn rabbit. Intravenous injection of 0.05 c.c. of 0.016 molar solution gave definite increase in rate and amplitude, while twice this amount was followed by convulsions. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously. Kymograph speed, 6 seconds = 1 centimeter.

Suckling Animals.—The respiratory responses were observed in a group of suckling animals in order to detect any marked alteration in reaction after survival for one to four weeks in the extrauterine environment. Pentobarbital sodium (20 to 30 mg. per kilogram) was injected subcutaneously an hour before the experiment. The results with the various drugs showed no striking change in sensitivity of the animals. The margin between the minimal effective dose and the convulsive dose remained about the same as was noted in the newborn. Observations were made with metrazol in 7 animals from 4 litters; with coramine in 6 animals from 4 litters; with caffeine in 2 animals of a litter; and with alpha-lobeline in 6 animals from 4 litters.

Late or delayed effects of the drugs were also investigated in addition to the immediate effect upon respiration as recorded by kymograph tracings. In view of the differences in rate of destruction or elimination of various drugs by the body, the animals were kept under observation for twelve hours or longer following injection. Failure to survive longer than a few hours following administration of the drug was noted frequently after alpha-lobeline, coramine, and caffeine. After metrazol and cyanide, however, the animals survived, despite the occurrence of convulsions.

Discussion

From the foregoing observations, three findings stand out clearly. First, it was difficult to demonstrate significant stimulation of respiration in the

sense of increase in rate and depth of breathing by the administration of alpha-lobeline, coramine, and caffeine; and following metrazol and cyanide, the slight stimulation was transient, lasting less than a minute. Second, a considerable hazard involved in the use of these drugs was found to be the narrow range between the dosage which affected respiration and that which caused convulsions. Two or three times the effective dose usually resulted in convulsions in animals which had received pentobarbital medication. In the absence of pentobarbital, the convulsive dose was smaller, being about one-half as great in the case of alpha-lobeline and caffeine, and about one-fifteenth as great in the case of coramine and metrazol. In the absence of premedication with barbiturate, a narrow range between an effective dose and a convulsive one was still demonstrable, although the threshold for the effects had shifted. Likewise, in the series of suckling animals, no marked change was noted in the range of safe dosage, which remained narrow even in the absence of premedication. Throughout the experiments, the minimal effective dose was determined in a given animal, and a fresh animal was used to determine the convulsive dose, thus eliminating any cumulative effect. Third, late toxic effects of certain of the drugs, alpha-lobeline, coramine, and caffeine, may result in the death of the animals after a period of hours following apparent recovery from convulsions. Survival occurred, however, after metrazol and cyanide despite the occurrence of convulsions.

In the presence of asphyxia the hazards involved in the use of respiratory stimulants are greatly increased. In the case of failure of resuscitation the question arises as to whether the dosage of the drug was adequate. It is well known that the threshold for an effective dose of these substances may be greatly raised by numerous anesthetic drugs which are administered during labor. Of significance in this connection is the finding in previous work that the fetus is peculiarly sensitive to anesthetic agents (Rosenfeld and Snyder, 1938[9]). When fetuses were observed directly through the wall of the unopened uterus, marked depression of the fetal respiratory responses occurred at a level of dosage at which maternal respiration showed little change. An additional factor to be considered in the etiology of fetal apnea at birth is anoxemia, which may be quite independent of narcosis (Snyder and Rosenfeld, 1937[10]). In the experiments on adult dogs in which extreme anoxia was induced rapidly by the breathing of 100 per cent helium instead of air, Eastman and Kreiselman[11] found that injection of alpha-lobeline, metrazol, or coramine failed to elicit a response until the anoxia was relieved by the administration of oxygen, whereupon convulsions appeared. In the emergency when resuscitation is required, repeated injections of the drugs may be prompted by weak or absent respiratory responses. High levels of dosage may be reached and the toxic action of these powerful agents may be elicited, although not recognizable immediately but only after delay of several hours. In brief, in asphyxia the respiratory responses of the newborn to these powerful agents may be masked; a level of dosage resulting in convulsions may be reached with little warning. The full extent of injury wrought by certain of these substances may be revealed only after a delay of several hours following injection.

In attempting to account for the considerable clinical trial which the respiratory stimulants have had in the treatment of asphyxia in the newborn infant, it is evident that evaluation of the success or failure of drug therapy has been difficult under conditions associated with birth. Uncertainty regarding the value of these drugs has not led to their total abandonment, however, but rather has resulted in the subordination of them to other methods of

resuscitation, especially various types of artificial respiration. What is significant is not so much that the slight or ineffective action of these drugs has been recognized, as that the toxicity of these powerful agents has often been overlooked.

The present experiments lend no support to the employment of alpha-lobeline, coramine, caffeine, metrazol, or cyanide in the resuscitation of the newborn infant. Outstanding factors influencing this conclusion are: (1) the relatively slight and transient nature of the increase in rate and depth of breathing elicited by these agents even under favorable circumstances; (2) the narrow range between an effective dose and one causing convulsions; (3) the shift of threshold for both the therapeutically effective and convulsive doses under the influence of narcosis and anoxemia, thereby confusing the calculation of dosage; (4) the insidious nature of the toxic action of certain of these drugs.

Conclusions

1. In newborn rabbits significant stimulation of respiration was difficult to demonstrate following alpha-lobeline, coramine, or caffeine; and following metrazol or cyanide the slight stimulation was transient, lasting less than a minute.

2. A considerable hazard involved in the use of these drugs was found to be the narrow range between the dosage which affected respiration and that which caused convulsions. Two or three times the effective dose usually resulted in convulsions in animals which had received pentobarbital premedication.

3. Injury resulting in death frequently followed convulsions which occurred after alpha-lobeline, coramine, and caffeine. Survival occurred after metrazol and cyanide despite the occurrence of convulsions.

4. The present experiments lend no support to the use of alpha-lobeline, coramine, caffeine, metrazol, or cyanide in the resuscitation of the newborn infant.

References

1. Comroe, J. H., and Schmidt, C. F.: Am. J. Physiol. **121**: 75, 1938.
2. Marshall, E. K., and Rosenfeld, M.: J. Pharmacol. & Exper. Therap. **59**: 222, 1937.
3. Werner, H. W., and Tatum, A. L.: J. Pharmacol. & Exper. Therap. **66**: 260, 1939.
4. Wilson, R. A., Torrey, M. A., and Johnson, K. S.: Surg., Gynec. & Obst. **65**: 601, 1937.
5. Russ, J. D., and Strong, R. A.: Am. J. Dis. Child. **61**: 1, 1941.
6. Stuppy, C.: Geburtsh. u. Frauenh. **2**: 528, 1940.
7. Dörr, H.: Monatschr. f. Geburtsh. u. Gynäk. **107**: 129, 1938.
8. Rosenfeld, M., and Snyder, F. F.: Am. J. Physiol. **121**: 242, 1938.
9. Rosenfeld, M., and Snyder, F. F.: Am. J. Obst. & Gynec. **38**: 424, 1939.
10. Snyder, F. F., and Rosenfeld, M.: Am. J. Physiol. **119**: 153, 1937.
11. Eastman, N. J., and Kreiselman, J.: Am. J. Obst. & Gynec. **41**: 260, 1941.
12. Nevinny, H.: Beilageheft zur Ztschr. f. Geburtsh. Gynäk. **114**: 1, 1937.

THERAPY IN HABITUAL ABORTION*

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ONE of the most discouraging problems in the entire field of obstetrics has been that of habitual abortion. As is so often the case where results are unsatisfactory, writers upon this subject disagree concerning everything from definition through etiology and treatment, even to the very advisability of trying to do anything.

While Shute[17] feels that one cannot surely recognize a habitual aborter until three or more successive pregnancies have terminated spontaneously at or before the sixteenth week, others are satisfied to make the diagnosis after two failures. As a matter of fact, one of my cases was treated after only one spontaneous abortion, but subsequent events, I feel, justify her inclusion in this report.

For obvious reasons, any exact figures on the incidence of spontaneous abortion, let alone habitual abortion, must be rather speculative. Malpas believes that 1 per cent of all pregnancies end in repeated abortions. Using this figure, the Council on Pharmacy and Chemistry of the American Medical Association[5] surmises that in the United States alone there would be upward of 24,000 and possibly as many as 48,000 habitual abortions a year. Startling as these figures may seem from the standpoint of loss of life, they are as nothing when compared to the heartaches in the homes of those families where pregnancy after pregnancy is achieved, only to be followed almost inexorably by one spontaneous abortion after another. As a result, these patients are ready to cooperate in any reasonable regime that may be offered.

Several competent observers,[11] by histopathologic study of series of abortuses, have reported abnormalities in from 50 to 80 per cent of them. This fact being admitted, the problem of accounting for it arises. Mall feels that all of them are due to faulty implantation, while Meyer is of the opinion that the cause lies in an abnormality of the germ cells, either in the ova or the spermatozoa. Corner,[11] from a study of reproduction in swine, takes a middle-of-the-road course. He failed to find any histologic evidence of implantation abnormality, a strong argument for the poor germ cell theory, but he quite readily admits the possibility of chemical lesions proceeding from altered secretions without visible cytologic changes.

What then should be our attitude, in view of these two equally scholarly but widely divergent views? Malpas,[1] from a study of 115 abortion and stillbirth sequences, concluded that after two successive abortions 62 per cent would have a normal third pregnancy, after three 27 per cent would go to term, while after four only 6 per cent would go to a successful conclusion without any specific treatment. Quoting these figures, Rock[12] is rather skeptical of the value of any treatment. Many others, however, are more optimistic and report a very low incidence of fetal abnormalities among their successful cases. These reports make treatment seem of very decided value. Furthermore, they lend strength to Mall's theory of faulty implantation, while casting very real

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doubt upon the defective germ cell theory of Meyer, at least in so far as it might be applied universally to habitual abortions.

Prior to 1918, all therapy was of an empirical nature and consisted primarily of rest in bed and sedation. In that year, J. C. Hirst of Philadelphia first began the use of an aqueous extract of corpus luteum. Since that time, others have attempted the use of one agent or another, with the hope of having a beneficial effect. Thus Rosenfeld[13] and others felt that the blood serum of these patients lacked something necessary for the normal continuation of pregnancy. What this lack might be was a matter of pure conjecture but a number of patients were carried to term when they were given blood serum from normal healthy gravidas.

Thyroid gland has been used wherever there was a low basal metabolic rate. In addition, many writers have advocated its administration in doses of from ¼ to 1 grain a day as a routine measure in all cases, with the thought that it might help correct other endocrine dysfunctions, notably in the corpus luteum.

Shute has found an antiproteolytic substance in the blood serum of those who were about to abort or miscarry. This condition has been corrected, in some cases, by the administration of vitamin E either as 2 to 5 drams daily of cold pressed wheat germ oil or, more recently, 20 to 50 mg. of synthetic alpha tocopherol. He feels that this is of less value, however, in patients who are early aborters than in those who tend to lose their pregnancy at a later period. Collins[4] was unable to get consistent or conclusive results by using Shute's method on the blood serum. He, nevertheless, felt that one should make every possible effort to carry a habitual aborter to term, and so, while the test was abandoned, he continued to use 1 to 1½ drams of wheat germ oil daily, with an increase to 8 to 12 drams if any evidence of threatened abortion appeared. This attitude is not far from accord with that of the Council on Pharmacy and Chemistry[5] which summarized its report by saying that, while vitamin E therapy seemed promising, the results up to that time (1940) were not conclusive.

If, as Shute claims,[16] the vitamin deficiency has a concomitant estrogen excess, that is, the antiproteolytic factor is estrogenic[15]; then progesterone, which might be called the physiologic antagonist of the latter,[6] should be our long sought specific. Since becoming commercially available, as might be expected, both natural and synthetic progesterones have been widely used in this connection. Several observers have found that at the beginning of pregnancy the corpus luteum is very active but, during the third month it begins to atrophy and its function, at least in so far as the elaboration of progestin is concerned, is taken over by the placenta. This change occurs somewhere between seventy and ninety days after conception and thus coincides with the period during which the large majority of habitual abortions occur. Hamblen[8] has found that the pregnandiol titers tend to fall either abruptly or gradually in most cases, prior to abortion. He has also been unable to elevate a low output or to prevent abortion by the administration of progesterone either alone or in combination with estrogens or chorionic gonadotropins. This writer consequently goes so far as to say that large doses of progesterone, by depressing the metabolism of intrinsic progestin, might precipitate abortion. Other writers such as Mason,[11] Campbell and Sevringhaus,[3] and MacGregor and Stewart[10] feel that progestin is of definite value.

If both vitamin E and progestin seem to be of value, the next logical step should be to combine them. Shute has done this with a number of his cases, as have others. Schmidt-Elmsdorff and Herold[14] even go so far as to state that vitamin E, by its support of the endocrine system, seems to enhance the effect of the progestin, thus accounting for their use of both.

Clinical application in threatened abortion, whether habitual or not, has presented certain definite drawbacks, and early reports have been extremely disappointing. Wheat germ oil, according to Shute,[16] must be fresh and given in adequate dosage to control the symptoms. While this is certainly a reasonable statement, to carry out its provisions is quite another matter. Hermetically sealed bottles of the oil may or may not be potent, while adequate dosage, as he has outlined it, becomes rather expensive if continued for a very long time. As for the three minim capsules so often used, adequate dosage almost resolves itself into a feat of deglutition. Shute has used a synthetic alpha tocopherol recently, but the patients to be mentioned later were given a mixture of alpha, beta, and gamma tocopherols distilled from vegetable oils and marketed as Tocopherex. Reasonably small doses of three to nine capsules or 9 to 27 drops a day sufficed. Since this series was begun, however, the manufacturer has withdrawn the liquid form from the market, so it is now available only in capsules, each containing 50 mg. of the mixture or the equivalent of 30 mg. of alpha tocopherol.

Another stumbling block in this combination therapy has been the unavoidable time lag between the onset of symptoms, whether cramps, bleeding, or both, and the administration of progestin to the patient. Irreparable damage may and probably does occur during this interval. This is particularly true in the event of bleeding, indicating, as it does, more or less separation of the chorionic attachment.

An experience with a threatened miscarriage pointed the way to a possible circumvention of this time lag in cases of habitual abortion. A primigravida in her sixth month was having frequent uterine contractions with the head well down in the pelvis and the cervix beginning to dilate. A hypodermic of morphine, ¼ grain, and an intramuscular injection of progestin in oil were given and she was left with a supply of 5 mg. tablets of anhydro-hydroxy-progesterone or pregneninolone. Her instructions were to take them three times a day and also at any time the cramps might recur. Although she had cramping for several days, each attack was promptly controlled by this oral medication, and after a week she was able to resume her regular normal activity. The pregnancy then proceeded uneventfully with the delivery of a normal girl just two days before her expected date.

The successful outcome of this case suggested the possibility of using this preparation in the prophylaxis of habitual abortion. As a result, the cases mentioned below were given 3 drops (or one capsule) of mixed tocopherols three times daily as soon as the first period was missed, 6 drops (two capsules) a dose for three days before the next period was due, 9 drops (three capsules) at a time during the days of the expected flow, tapering off with 6 drop doses for another three days, and then returning to the 3 drop level until time for the next period. This regime was continued at least until definite fetal movements were felt by the patient. The dose was also promptly increased to the 9 drop level in the event of either cramps or bleeding. Oral pregneninolone or pranone was also given in 5 mg. doses on the first three days of each expected period prior to quickening, plus an immediate dose should any evidence of threatened abortion occur. All patients were told to carry one or more tablets with them at all times and, in the event of either cramps or bleeding, to take a tablet, get off their feet, and call me. The emphasis was placed upon taking

the medication immediately. All were cautioned against undue exertion at any time and advised to take extra rest at the time of expected periods. All intercourse was prohibited. Thyroid was given to some but only as noted below.

Case Histories

CASE 1.—Mrs. M. L., aged 23 years, para O, gravida ii. First visit in this pregnancy Nov. 15, 1941 with her last menstrual period September 29. Six months prior to this she had had a spontaneous abortion on the eighty-first day, and had been advised to report as soon as a period was missed. There had been no special studies beyond physical and routine postpartum examinations. These were negative except for a very slight degree of endocervicitis. At this time she was put on the routine as outlined above. In spite of this she had slight cramps and spotting beginning on the eighty-second day and continuing for several days thereafter. Bed rest and the treatment already outlined resulted in a cessation of these symptoms, and she continued with an uneventful course and a normal boy delivered eighteen days prior to the expected date. This was the first case treated by this routine, and she has been included as an habitual aborter for three reasons. First she had one spontaneous abortion, second she had a threatened abortion while under treatment, and finally, when a third conception occurred a few months later, she did not bother to take any treatment and had a second spontaneous abortion.

CASE 2.—Mrs. H. W., aged 35 years, para i, gravida iv. First pregnancy normal, with a boy aged 13 years. During the depression she had used contraceptives. She first consulted me in her second pregnancy which was uneventful until the 110th day when she began to have cramps and a bloody discharge. In spite of bed rest, wheat germ oil, paregoric, and intramuscular injections of progestin at home, she continued to have these symptoms until they ended in an abortion on the 115th day. During her third gestation she began to take wheat germ oil at the start and was also given progestin at home from the onset of cramps on the 53rd day. In spite of this she miscarried on the 78th day. Following this second failure her basal metabolic rate was found to be −23 per cent. This was surprising as, clinically, she seemed to be exactly the opposite. On 1 grain of thyroid daily this was raised to −4 per cent, and the patient again attempted a pregnancy. This time she was given mixed tocopherols and pregneninolone in addition to her thyroid. She had both cramps and bleeding several times during the first five months but the pregnancy continued with delivery of a normal boy six days after the calculated date. She has had no further pregnancies.

CASE 3.—Mrs. G. W., aged 27 years, para O, gravida iv. First miscarriage was spontaneous at about the second month. A second one occurred at about six weeks. With her third pregnancy she began taking wheat germ oil at once and was given progestin at the second period time and again at home on the 77th day when she began to have a bloody discharge. This was to no avail as she aborted about fourteen hours later. Sterility studies seemed normal, and, because of many steps where she was living, she was advised to move. During her fourth pregnancy she took tocopherex from the start and pranone at period times and also as needed for cramps. This pregnancy resulted in a normal male infant five days beyond the expected date. No further pregnancies.

CASE 4.—Mrs. D. McK., aged 26 years, para O, gravida iii. She had miscarried at three and a half months, previous to moving to Pittsburgh. At her first visit in her second pregnancy, she was put on wheat germ oil and was given progestin at home on the 81st day for pains. She miscarried the following day. Sterility studies showed nothing abnormal except a −9 per cent basal metabolic rate. For this she was given ¼ grain of thyroid daily and also advised to move from the steep hill upon which she was living. With her third pregnancy she began taking mixed tocopherols as soon as her first period was missed, plus pregneninolone at period times and as needed for symptoms. She had a little bleeding at the time of her second period and some cramps at the third. After that she continued uneventfully to term, with delivery of a normal boy seventeen days after the calculated date. No further pregnancies.

CASE 5.—Mrs. A. C., aged 27 years, para O, gravida iv. Wheat germ oil and paregoric were advised for pink discharge on the 77th day of her first pregnancy, with abortion on the 81st day. She took wheat germ oil from the start of her second pregnancy but

aborted on the 73rd day. Thyroid, ¼ grain every other day, was begun for a −8 per cent basal metabolic rate. This was continued during her third pregnancy, together with wheat germ oil and pranone as needed. Nevertheless, she aborted on the 83rd day with the pathologist reporting a normal fetus. Four months later her basal metabolism was still −9 per cent, so her thyroid was doubled. All other studies were negative. With her fourth pregnancy she continued her thyroid through the fourth month. Tocopherex was taken for seven months and pranone at period times and as needed for cramps. She had several episodes of cramps and spotting during the first four months, but the pregnancy even survived the shock of having her brother reported missing in action (at the seventh month), and resulted in a normal living boy eleven days after the expected date.

CASE 6.—Mrs. M. A. L., aged 28 years, para i, gravida v. Her first pregnancy was uneventful, with a normal boy now 5 years of age. Her second ended in a spontaneous abortion at the third month. At about the fifth month of her third pregnancy there was so much abdominal tenderness that a laparotomy was done for a suspected ectopic gestation and she aborted a few days later. I first saw her with an incomplete abortion at about the third month of her fourth pregnancy. Following this, a general checkup failed to reveal any abnormality except a basal metabolic rate of −2 per cent. She was accordingly put on thyroid, ¼ grain daily, in addition to taking small daily doses of tocopherex before beginning her fifth pregnancy. In spite of this she had pain and tenderness in the left cornua together with spotting about six weeks after her last menstrual period. As a result she was hospitalized, and I too had a fear of a tubal pregnancy. While in the hospital she was given progestin in oil but after discharge she reverted to the oral pranone. Her tocopherol intake was, of course, stepped up to the upper level of dosage and on this regime her tenderness fully subsided. One further episode of watery discharge, probably urine, at the fourth month, kept us anxious for a few days, but from that time on everything proceeded smoothly. She continued her medication until within a month of term and delivered a normal girl five days after the calculated date.

Summary

Admittedly, the above is a short series of cases, yet the complete success in six pregnancies, where a total of sixteen previous pregnancies had yielded but two living babies, would seem very promising even if not necessarily conclusive. All patients but two (Cases 1 and 6) had had treatment in at least one prior unsuccessful pregnancy. Four of them were given desiccated thyroid in addition to the two preparations mentioned. One of these and one other were advised to move to avoid excessive climbs, but two others were successful in spite of steep hills and many stairs. Thus it might be postulated that thyroid is not indicated routinely but only in the presence of a lowered basal metabolic rate. Likewise environment is worthy of consideration, especially in a city having many hills and steep steps as does Pittsburgh.

These and any other indicated corrective measures should, of course, be employed. Yet it would seem that the principal basis for success rests with the combination of a potent preparation of vitamin E started in the very beginning or before, together with progestin or, rather, a progestin-like effect immediately available when needed.

The preparation of mixed tocopherols used in the above cases seems to have two very necessary properties. First, it seems to be reasonably stable, even in the liquid form. Second, its effect may be achieved without heroic-sized doses.

A progestin-like effect, in so far as the control of uterine contractions is concerned, can be obtained by the oral administration of pregneninolone. This avoids the necessity of trips to the physician's office at period time which is just when the patient should try to spare herself any unnecessary activity. It also has the added advantage of being constantly available should the patient begin to have any cramps or bleeding.

No ill effects were noted in the above series which might be ascribed to either of the preparations used. An interesting sidelight, however, is that five of the six successful pregnancies continued until after their expected dates.

Successful treatment of threatened abortion cannot be expected unless one does as Krohn and Harris,[9] who provided each patient in their series with a supply of pregneninolone at the time of her first visit. Such a method would probably be of value in drastically reducing the incidence of spontaneous abortion, although I doubt its practicability as a routine measure. Anything short of this measure would probably be of little help, as, in my experience, these preparations are very seldom successful when begun after the onset of symptoms.

Conclusions

1. A combination of mixed tocopherols (Tocopherex) and oral pregneninolone (Pranone) has proved successful in a series of six cases of habitual abortion.

2. Treatment must be begun before the onset of any signs of threatened abortion, preferably as soon as the first period is missed or, better yet, as soon as a pregnancy is attempted.

3. This treatment is to be used in conjunction with, but not to replace, other indicated corrective measures. It is interesting to note, however, that no sedatives nor narcotics were found necessary.

4. No ill effects were observed, and all babies were normal.

5. This treatment is for the particular pregnancy, and probably will have no beneficial effects upon any future pregnancy.

References

1. Bachrach, A. L.: Brit. M. J. **1**: 890, 1940.
2. Beavers, Herbert: Texas State J. Med. **36**: 730, 1941.
3. Campbell, Ralph E., and Sevringhaus, Elmer L.: Am. J. Obst. & Gynec. **39**: 573, 1940.
4. Collins, C. G., Weed, J. C., and Collins, J. H.: Surg., Gynec. & Obst. **70**: 783, 1940.
5. Council on Pharmacy and Chemistry: J. A. M. A. **114**: 2214, 1940.
6. Council on Pharmacy and Chemistry: J. A. M. A. **116**: 1523, 1941.
7. Falls, F. H.: Surg., Gynec. & Obst. **75**: 289, 1942.
8. Hamblen, E. C.: Am. J. Obst. & Gynec. **41**: 664, 1941.
9. Krohn, Leon, and Harris, Joseph M.: Am. J. Obst. & Gynec. **41**: 95, 1941.
10. MacGregor, T. N., and Stewart, C. P.: J. Obst. & Gynaec. Brit. Emp. **46**: 857, 1939.
11. Mason, Lyman W.: Am. J. Obst. & Gynec. **44**: 630, 1942.
12. Rock, John: New England J. Med. **223**: 1020, 1940.
13. Rosenfeld, Samuel S.: New York State J. Med. **38**: 440, 1938.
14. Schmidt-Elmsdorff, H. R., and Herold, L.: Therap. d. Gegenw. **81**: 11, 1940.
15. Shute, Evan: Am. J. Obst. & Gynec. **35**: 249, 1938.
16. Shute, Evan: Surg., Gynec. & Obst. **75**: 515, 1942.
17. Shute, Evan: J. Obst. & Gynaec. Brit. Emp. **49**: 534, 1942.

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CATHARINA GEERTRUIDA SCHRADERS AND HER DIARY*

A Note on the History of Obstetrics and Especially on the History of Placenta Previa

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THE composition of a diary has not been an uncommon product of the pen in many of history's ages. Much information about English life under the last Stuart rulers and William III may be obtained from the diary of John Evelyn. A more breezy and intimate mixture of incidents occurring during the first nine years of the Restoration may be sought in the now famous diary of Samuel Pepys. Diaries are not only sources of considerable historical interest and importance but in addition may attain, as Evelyn's and Pepys' have, a worthy place in the field of literature. Spanning the closing years of the sixteen hundreds and the greater part of the first half of the seventeen hundreds, another diary was written, written by a midwife. It is far from a literary achievement, but it is unique insofar as it portrays life in a community in the north of Holland and records the experiences of a woman dedicating about fifty years of her life to midwifery. It discloses facts that are a contribution to the history of obstetrics and especially to the history of placenta previa. Catharina Geertruida Schraders becomes more unique because until now she has escaped our notice and, except for two relatively short articles written about her, and the diary by two of her own countrymen, Dr. Arie Geyl of Dordrecht and Dr. Nuyens of Amsterdam, she has rested in oblivion.

Interest in the bibliography of the history of placenta previa led me to Geyl's paper, which was entitled "Catarina Gertruyt Schraders. Investigator of the Anatomical Character of Placenta Previa." This article, written in French, appeared in *Janus* in 1897 and informs us that Madam Schraders was among the first to investigate and appreciate the anatomic nature and clinical significance of placenta previa. Dr. Nuyens' article was published in 1926 in the *Nederlandsch Tijdschrift voor Geneeskunde* (the Netherlands Journal of Medicine). His paper, written in Dutch and entitled: "The Diary of Madam Schraders. A Contribution to the History of Midwifery in the Seventeenth and Eighteenth Centuries," is longer than Geyl's, has much more to say about the diary, and is more biographical and informative. It should be pointed out that these two references are the only available sources of information that concern the subject of this paper. Consequently, the substance of the story as it is told here is drawn almost entirely from the translation of these two articles, especially that of Nuyens. To Dr. Adriaan Barnouw, Professor of Dutch at Columbia University, the author wishes to express his thanks and gratitude for the invaluable assistance rendered in the translation of Madam Schraders' original passages and excerpts as they appeared in Nuyens' article. Originally, the hope was cherished that a photostatic copy of the entire diary might be procured from the Library of the University of Amsterdam in order that it might be translated and edited in the English language. However, when the request was made in February of 1940, the following reply dated March 9 was received from the librarian: ". . . we regret to inform you that in consequence of the international circumstances all our valuables are safely packed up,

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so that it is impossible to make photostatic copies of the Diary of Catharina Geertruida Schraders for you." Holland was invaded exactly sixty-two days later, on May 10.

First, let us consider a description and the disposition of the diary. According to Nuyens, one cannot attribute any beauty or elegance to its external appearance. The binding, obviously never meant to be a permanent one, simply consists of cardboard, and not of the period in which the diary was written. It is clear that it could be replaced when necessary. The diary is 544 pages long and is written entirely on fine solid old Dutch paper which has withstood a period of over two and one-half centuries without damage or deterioration except for an occasional wormhole. Here and there the ink is somewhat faded, but is still sufficiently clear for reading. Throughout, the script is by the same hand, even though at the age of 90 it is not so evenly written as fifty years earlier. Occasionally a page is found to be torn, but fortunately the text is left undamaged. The diary begins without an introduction or inscription and ends as abruptly on page 544 without a postscript.

This remarkable manuscript was bequeathed to the library of the Netherland Association for the Advancement of Medicine by Dr. J. J. Kiestra, physician from Ee near Dockum in Friesland. The collection of books and manuscripts belonging to this Association was stored in the Library of the University of Amsterdam. Dr. Kiestra had purchased the diary from the previous owner, Sybrand Fockema, physician of Leeuwarden, who had inherited it from Daam Fockema. The diary came into Daam Fockema's possession as a result of her marriage to Wytske Higt (b. 1710, d. 1780), a descendant of Thomas Higt who married Catharina Geertruida Schraders in 1713 and thereby became her second husband.

Catharina Geertruida Schraders was born in 1655. The name of her birthplace is not mentioned. She lived in Hallum in Friesland and married Ernst Willem Cramers. According to one of her notations, he was a surgeon. Cramers died on Feb. 4, 1692, whereupon in 1693 she began to practice midwifery. Why and under what circumstances she made such a decision is better related in her own words:

"In my 38th year, I was living at Hallum in Friesland where I had seen my good and learned husband, who was esteemed and loved by God and men, depart to his God to the great sorrow of myself and the inhabitants, leaving behind six little children when I was 36 years old. But then it pleased the Lord to select me for this important work, almost through the coercion of the good doctors and citizens, against which I had first offered resistance because it was such a grave matter and because I also thought that it was somewhat of a disgrace for myself and my relations, but in the end I have let myself be persuaded, besides it was pleasing to the Lord."

From the diary it is learned that she did her first delivery on Jan. 9, 1693. It was not an easy one to begin with, since she encountered a face presentation and a retained placenta, but in the end all went well. The doctors and citizens of her community, whose advice she had followed, were well aware of her ability. However, it remains unknown where and how she acquired the knowledge to practice. In former days the wife of a surgeon not infrequently was or became a midwife. It is very possible that she was instructed by her husband who was not only a surgeon but also, from her own words, "learned." Furthermore, the environs of Hallum were not devoid of some good scientific influence and progress, for van Deventer lived in Wieuwerd until 1690, while the skillful Cyprianus was professor at Franeker.

As soon as she had become established and settled as an accoucheur, she made a brief annotation of every delivery and would mention the name of the father and mother, the sex of the child, and the remuneration received for her services in each case. Whenever she was confronted with an unusual or difficult problem, she would make ample notes of it. At the end of each year, she added up her earnings, sometimes noted the expenditures, and then began the new year with a devout prayer. She was a minister's daughter and very religious.

On page 439 of the diary, one has evidence of some of the difficulties and hardships that she experienced in her obstetric practice in the rural districts. In 1693 she was called to help a widow at Wyns:

"On a Tuesday in 1693, I was called for the first time to Wyns to aid a widow whose husband had been Nicholas Jansen. A terrible storm was raging with a severe sleet. The three of us drove in a sleigh across the ice and could not keep on one's feet on account of the wind. Frozen branches hurt my legs so that the blood ran in my stockings. We finally reached Wyns after three hours' driving. We were almost dead and they carried me in and gave me brandywine. There was a good fire in the house which thawed me out a little. I asked for a box of snow with which I rubbed my hands and feet so long that at last life came back, otherwise I should have been crippled for the rest of my life. Having recovered I could also help the woman. The patient's late husband's brother had taken everything away from her and had told her that she should not bear the child. Hence, much depended upon the child's life, as it always does. The woman had a very difficult delivery as in a previous delivery at which she had the help of two midwives from Leeuwarden. I prayed to the Lord, and He heard me, and delivered the woman to the great joy of herself and me of a fine big daughter. This introduction to obstetrics was a painful one, but the Lord be praised, all was well and the woman recovered all her property."

The diary also reveals that she soon developed a widespread practice. On Oct. 6, 1694, she was summoned to Ameland for the delivery of twins and she wrote: "I had to go across the sea. When I entered the house, she raised up and said to me 'good woman, you came too late' and with that she died suddenly which frightened me. Oh, poor martyrs who come under such tortures of midwives!" That last exclamation betrays the fact that Schraders, too, was aware of the miserable and inadequate training of midwives, as well as how disreputable some of them were.

In 1693 she moved to Dockum. Ever faithful to her custom of indicating the occupation or profession of the husband of her patients, one learns that her practice included all ranks of society. Next to the name of a laborer or skipper, merchant or minister, physician or surgeon one finds representative names of some of the old noble families of Holland—the Harinxma's, van Ayluwa's, van Heert Tot Eversberg, Burmania's.

The first year of her practice in Dockum was the most profitable. On Jan. 1, 1699, she stated that during the successful year of 1698 she delivered 123 women from whom she received 310 guilders and 10 stivers. For surgery she received 103 guilders and 16 stivers, for cupping 22 guilders. She noted that there were twenty-three women from whom she got no pay. Other revenue which amounted to 16 guilders and 6 stivers brought the total income for that year to 452 guilders and 12 stibers. As Nuyens remarks, the bookkeeping was very primitive, but the addition sound. The remuneration for her services was niggardly. For instance, her maternity work was paid with single guilders and stivers, and the journey to Ameland only brought her five guilders. Only the nobility paid well, but then she frequently would remain a few weeks with a lying-in woman and consequently she would lose several other deliveries.

During January, February, and March of 1698 she delivered forty women, almost three a week. Considering the circumstances, such a striking capacity and energy for work merits one's admiration. It is further disclosed in the diary that she received patients in her home, for on May 2, 1701, she noted that Elizabeth Dhrooge, the wife of a coppersmith, Arnoldus Dhrooge, came to her house and was delivered there of a daughter for which she received 2 guilders and 10 stivers. On April 20 of the same year, she wrote that a lady from Gullickstaedt came to her saying that she was the wife of the secretary of the King of Denmark—"I delivered her of a boy. I was godmother to the child and he was named Jacob. Nine guilders and 16 stivers." It is interesting that the fee for the delivery of the wife of the King of Denmark's secretary was almost four times that of the coppersmith's wife.

In this brief but precise style, the diary goes on year after year. She took note of every special incident associated with a delivery and at the end of the year mentioned the results. At the beginning of 1703, she stated that at the age of 47 and after completing ten years of practice, she had delivered 840 children. On page 243 of the diary one reads that after eighteen years of practice, when she was 57 years old, she had delivered 1,937 babies for which she was paid 4,300 guilders.

Suddenly, in 1713, the continuity of the diary was interrupted. One notes, however, that a single delivery was done on January 13. She married Thomas Higt, aged 63, on February 13. By profession he was a gold- and silversmith and a member of the Assembly of Dockum. Madam Schraders was then 58 years old. In 1714 she remarked: "In my married state I aided a few in dire need." Her second husband died in 1721 and immediately after she resumed her practice. Except for this short interim while she was married to Thomas Higt, she kept up her work and diary for about a half century, up to 1745.

The first new annotation after she resumed practice was remarkable. On Sept. 26, 1721, a Mrs. Pousma, the wife of a cavalry captain, was delivered of a daughter and much to her amazement, six weeks later was delivered of a dead son. In the beginning of her second widowhood she was not too busy. This may be explained by the fact that many pregnant women had secured help from others. In 1723, for example, she had only twenty-three deliveries and in 1724 thirty-five. The year of 1727 was opened with a lamentation. She had reached the age of 72 and things were not going too well with her. More because of her old age, she invoked the help of God to supply the means for her relief and subsistence. Fortunately, she did have a better income that year. She assisted 73 women and earned 225 guilders. Beneath this income is found her expenditures which amounted to 220 guilders. It is noteworthy that nothing could stop her from carrying on her work, for it is also observed that during that same year she was very ill.

A most interesting notation is found on page 330. It has nothing to do with her work, but gives us an insight into the cost of living at that time. It is a small bill from Mrs. van Ayluwa for meat which was delivered to Madam Schraders. "In March she sent a calf's head, 6 stivers; in June she sent 17½ pounds of mutton at a half a stiver per pound." Living certainly was not expensive.

In 1733 she summarized her work and noted that at the age of 78 she had collected 8,500 guilders for "doctoring" and 1,100 guilders for surgery, "... and the Lord's blessings have been upon me." Even though one's living main-

tenance apparently was not costly in those days, nevertheless the sum of 10,000 guilders that she earned during forty years of hard work is small. Her practice diminished gradually. In 1738 she had only 14 deliveries; in 1740, 13 deliveries; in 1742, 18 deliveries. Her last notation appeared on Feb. 7, 1745, when she had attained the age of ninety. Her handwriting was still as legible and vigorous as it was fifty years earlier. Her obstetric career began with the delivery of a face presentation and ended with a transverse presentation.

Death was not so sudden as the beginning and the ending of her diary, for Catharina Geertruida Schraders did not die until Oct. 30, 1746, at the age of ninety-one.

Here is a woman then who for approximately half a century, and at times under the most trying circumstance, practiced midwifery in a community in Holland and among all ranks of society. A midwife who by the time she was 85 years old, as she stated on Sept. 18, 1740, had delivered 4,000 babies among them 64 sets of twins and three sets of triplets. Furthermore, she was one who always kept careful and exact notes of her work, revealing how seriously she persevered in her task. If she were known only for these deeds, that should be sufficient to acclaim our admiration. But she reaches the higher levels of our esteem, especially as an accoucheur, when one considers and analyzes the results of her work and the manner in which obstetrics was practiced in the seventeenth and eighteenth centuries. Up to this point, beginning with the description of the diary, what has been written is essentially a translation of Nuyens.

Let us cast a glance at the obstetrics of Madam Schraders' time. According to Miller, the two centuries between 1525 and 1725 in the history of obstetrics are thought of as the period of transition linking ancient or female midwifery to modern or male midwifery. Thus, it is a happy circumstance that Madam Schraders should fall in the last days of that revolutionary and evolutionary epoch of midwifery which ultimately flowered into the modern or scientific era of obstetrics. For centuries, after the best influences of Greek medicine had waned and were lost, and after Paul of Aegina who was the last of the few more noteworthy Greek authors on gynecology and obstetrics had died in 690, women alone governed the lying-in chamber, whereas men in the adjoining room looked at the horoscope and the stars. Pregnant women were committed to the ignorance, superstition, incantations, and barbaric practices of midwives during this gray antiquity. Later, true enough, men were called in for help in the most difficult cases, but obstetrics still was practiced by women. Thorndike points out and wishes to emphasize the fact that at the close of the sixteenth century superstitious ceremonial and magical rites and incantations had diminished greatly, so that the road to mathematical and scientific method was opened. Medicine and surgery began to make rapid strides in scientific progress, but obstetrics lagged behind. As a consequence, numerous pregnant women and many more babies continued to be the sacrifices of the ignorant and badly instructed midwife. In unfavorable outcomes these midwives were overburdened with reproach and abusive words, and not the least by surgeons. However, it is questionable whether these same surgeons who occasionally were invoked for assistance ever contributed anything constructive. They knew little more about obstetrics than the midwives whom they scorned.

The status of the midwife began to change with the appearance of Rösslin's *Rosengarten* in 1513. This was the first textbook on obstetrics that midwives had ever had to consult for their instruction. Walter Reiff's *Frawen Rosengarten* (1545) and Jacob Rueff's *Trostbüchle* (1554) were two of the better

known works that appeared after Rösslin's. Originally written in the vernacular, these treatises were translated into many languages and passed through numerous editions. However inadequate and unoriginal these early textbooks and their translations were, an influence was initiated in the proper direction inasmuch as they were written for the guidance and improvement of the midwife. Vesalius' *De Fabrica,* the works of Falloppio, Fabricius ab Aquapendente, Aranzio, and many other anatomists advanced the knowledge of female anatomy. As the knowledge and appreciation of female pelvic anatomy increased, surgeons began to turn more of their attention to obstetrics. In France, Ambroise Paré rediscovered version and extraction, Guillemeau further promulgated its use, and François Mauriceau entirely abandoned the practice of surgery to make a specialty of obstetrics. Scipio Mercurio in Italy became the first to state that a contracted pelvis was a definite indication for cesarean section. In Holland, van Deventer practiced orthopedics and obstetrics and now is acclaimed "the father of modern midwifery." William Harvey advanced the cause of obstetrics in England. Jules Clement with the indorsement and blessings of Louis XIV ultimately broke down the prejudices against the man midwife and established his place in the delivery room. Finally, the excellent textbooks of Mauriceau, Portal, de la Motte, and van Deventer raised obstetrics from its debased position and placed it, as Miller puts it, "on the road of true scientific reform based on exact knowledge and rational principles." In Holland the practice of obstetrics remained in the hands of midwives almost to the last years of the eighteenth century.

The criticism and condemnation directed toward midwives continues to be vehement. None could be more violent than Geyl's in a study on the instruction of midwives which he published in 1897. That there is justification in the greater part of this condemnation is unquestioned. Among the innumerable badly instructed and unscrupulous ones, however, there must have been a considerable number of good and able midwives deserving more than the contempt which was universally thrown at them just because they were midwives. Recall that even Madam Schraders first resisted the idea of becoming a midwife "because I also thought that it was somewhat of a disgrace for myself and my relations."

It was centuries before any one of them rose above the average capacity and ability of her sisters, but the close of the sixteenth century produced Louise Bourgeois; the last years of the seventeenth, Justine Siegemundin; late in the eighteenth century, Madame du Cordray; and in the beginning of the nineteenth century, Madame La Chapelle and Madame Boivin. Each one of these famous midwives, in addition, wrote a book on obstetrics meriting a place beside those of her male competitors.

It appeared necessary to insert this brief perspective of the historical background of the state and development of midwifery during Madam Schraders' time in order that she and an analysis of her work and results might be better projected and evaluated.

This pious, honest, modest, and conscientious woman says nothing about asepsis or antisepsis, nothing about narcosis in her diary. The use of forceps was little known if at all. In 4,000 cases, the placenta was found adherent 65 times. Credé's maneuver did not exist then, but she employed the procedure of inserting her right hand into the uterine cavity to separate and remove the placenta while the cord was held in the left hand, a method which was recommended by van Deventer, Portal, and others as a good one. She records 90 fetal

deaths, a fetal mortality of 2.25 per cent in 4,000 deliveries, which is creditable to say the least. Among the causes are mentioned: prolapsed cord 25 times, placenta previa several times, transverse presentations, obliquely contracted pelves, breech presentations, and monsters. There were 15 maternal deaths or a maternal mortality of 0.375 per cent (nearly four per thousand). On three occasions she was called and the mother was found moribund, on one occasion the mother was already dead. For the rest, puerperal infection is mentioned six times as the cause of the death of the mother, placenta previa (hemorrhage) twice, and tuberculosis of the lungs, convulsions (eclampsia?) and gangrene of the leg once each. Such an outcome is remarkable. It is impressive to note that the number of cases of infection is small. No word is mentioned of a special solution for the hands; but oil, butter, or green soap were ordered as a lubricant. It is possible, too, that the particular rural environment supplied a natural immunity to keep the fatal outcome of puerperal infection low. If her results are compared to those of the Maternité in Paris where the maternal mortality rate was between 10 per cent and 16 per cent during the eighteenth century, as Nuyens points out, even Geyl would admit that a pregnant woman was safer in the hands of the scorned and reviled midwife.

Only on eight occasions did she call upon the help of a surgeon.

She made a distinction between "the hook" and "the instrument."

It is clearly observed in her diary that she knew and followed van Deventer's *Novum Lumen* which was published in 1701.

She knew version and extraction, and it is extraordinary and of the greatest interest to obstetric history how she promptly understood the anatomic relationship and clinical implications of placenta previa as soon as she was confronted by this complication. She encountered her first case in August of 1701 and wrote:

"I was summoned to Hylles, to the wife of a merchant Rinck Eckes, after I had been called there several times because she had a hemorrhage; and when I was called the last time, I found her very weak and with intermittent large losses of blood, but finally she fell into labor; when I examined the case, I found the placenta ahead of the baby, but adherent, something which I had never heard mentioned nor which I had ever before experienced; I was obliged to peel it off; the baby was found lying across the cervix; I turned it and succeeded with a great deal of difficulty in extracting it by the feet; but the infant was already dead and the mother died a half hour later." Five years later she had the second case of placenta previa on August 1. She noted: "I found the placenta firmly adherent, in front of the baby; I prescribed immediate delivery, but asked for the assistance of a doctor. She was not in labor. The doctor stated that he wished to give her something to start labor. I said the baby was dead, he maintained that it was alive; I pushed aside the placenta after having detached it, found the feet and extracted the child to Dr. Eysma's shame who had insisted that the child was alive whereas it had already shown signs of maceration."

On Dec. 1, 1724, Gerrit Creemers de Ternaart consulted Madam Schraders about his wife who had been having continuous losses of blood for two weeks to the point where she would faint. Without hesitation she advised that the patient be delivered at once by the midwife in attendance. The midwife requested to know whether Madam Schraders had lost her mind in advising the delivery of a woman who had not yet begun labor. She lost no time in making any reply, but promptly went to the patient herself and when her colleague obstinately refused to follow her advice, then she took over and began the delivery. She found the placenta attached to the lower part of the uterus, detached it and

soon after the mother was delivered and saved. The baby was already dead. Geyl states that she reported six real cases of placenta previa and one doubtful one. At the time of her first case she waited until labor set in before attempting any exploration and action, but having in mind the fatal outcome of that case she acted more promptly thereafter. She was convinced that placenta previa should be treated at once regardless of labor or cervical dilatation and adopted the maxim: Act as soon as hemorrhage menaces to be fatal. It was not long ago that accouchement forcé was the form of therapy accepted and recommended by many distinguished and able obstetricians to combat placenta previa.

According to Fasbender, there can be no doubt that Paul Portal was the first to recognize the clinical significance and anatomic relationship of placenta previa. His *La Pratique des Accouchemens,* etc., was published in Paris in 1685. Haller translated it in Dutch in 1690. Portal's first observation on placenta previa occurred in 1672. Madam Schraders' first experience with placenta previa was dated August, 1701 twenty-nine years after Portal's first case, sixteen years after the appearance of his book, and eleven years after Haller's Dutch translation of it was published. Could Portal's *La Pratique* or Haller's translation of it have crossed her path? We believe not. Her own words state, as she described the findings in her first case, that it was something which she had never heard mentioned nor which she had ever before experienced. Geyl asserts that Madam Schraders recognized the condition independently of Portal, and that she and Portal not only pointed out the anatomy of placenta previa, but also recognized the clinical danger associated with it and understood the means to combat it.

With Nuyens this author is agreed when he writes that if Catharina Geertruida Schraders had been less modest and had lived in other surroundings, if she could have been better able to express herself in the language of the art of midwifery and had sought a publisher, then she might have given to posterity a book as good as most of her time. True, she did not write a handbook nor a treatise for midwives, but she did write a diary. Had her case reports ever been published, she might have acquired a name in the history of obstetrics worthy to be placed next to those of Bourgeois, Siegemundin, La Chapelle, Boivin, and others. She certainly was not less capable. Her diary gives us an insight into a remarkable human life and into the difficulties and hard existence of an ingenuous midwife who nevertheless by her wisdom practiced her calling. Her careful notations and her untiring work merit the recognition, gratitude, and admiration of posterity.

References

Nuyens, B. W. Th.: Het Dagboek van Vrouw Schraders. Nederl. Tijdschr. v. Geneesk. **70**: 1790, 1926.

Geyl, A.: Catarina Gertruyt Schraders, Janus **1**: 537, 1896.

Miller, J. L.: Renaissance Midwifery: The Evolution of Modern Obstetrics, 1500-1700. Lectures on the History of Medicine, Mayo Foundation Lectures, Philadelphia, 1933, W. B. Saunders Co.

Fasbender, H.: Geschichte der Gerburtschülfe, Jena, 1906, Gustav Fischer.

Garrison, F. H.: An Introduction to the History of Medicine, Philadelphia, 1924, W. B. Saunders Co.

PATHOGENESIS OF POSTABORTAL PERITONITIS

A Study of 61 Cases

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DURING the past fifteen years an intensive study of the clinical and pathologic aspects of the incomplete abortion has been conducted in this service. From this study two conclusions were reached. First, the uterine cavity is usually infected in incomplete abortions, whether spontaneous or induced, with or without fever. Second, all infected abortions may be divided into six groups depending on the pathology found and their clinical course.[1]

These six groups are:

1. Abortion in which the infection is limited to the cavity of the uterus, which comprises 83 per cent of all abortions seen.

2. Abortion in which the infection spreads from the uterus but is still limited to the extraperitoneal structures. About 9 per cent of all abortions are of this group, which includes parametritis, pelvic cellulitis, extraperitoneal pelvic abscess, perivesical and perirectal exudates, etc.

3. Abortion in which the infection spreads from the uterus to the veins and where the predominant symptoms are the result of thrombophlebitis, with or without embolization. Parametritis is frequently an associated or causative lesion.

4. Abortion in which pathogenic bacteria have left the uterus and become secondarily implanted on the mural endocardium, heart valves, or pulmonary artery, and the infection is disseminated from this location. Visible evidence of either a pre-existing pregnancy or of infection in the uterus is often absent at autopsy.

5. Abortion in which the infection spreads from the uterus to the peritoneeum, producing a general peritonitis.

6. Those cases in which the uterus has been perforated by an instrument. The pathologic findings depend upon the degree of infection, asepsis, trauma to adjacent organs, etc.

This present study is devoted to an analysis of the pathogenesis and the associated pathologic findings in the fifth group, i.e., general peritonitis. Many gynecologists include patients with parametritis and an associated peritoneal edema or local pelvic peritonitis in this group. The inclusion of such patients among those with generalized peritonitis is unsound from the viewpoints of the pathogenesis and morbid anatomy. Furthermore, a false impression is created in respect to the prognosis and the efficacy of treatment. The following discussion is therefore limited to those patients in whom generalized peritonitis followed abortion (exclusive of those secondary to perforation of the uterus.)

To formulate a concept of the problems of diagnosis and therapy of postabortal peritonitis, it is important to determine how the infection spreads from the endometrium to the peritoneum. At necropsy only the end stages of the disease are evident; on the other hand, a clear analysis of the pathway of the infection during life may be impossible.

In postabortal disease the infectious process begins almost exclusively at the placental site and in the adjacent endometrium. This area is the seat of a suppurative process and may be converted in whole or in part into a shaggy, inflamed, or necrotic membrane to which portions of placenta, decidua, and blood are adherent. On microscopic examination there is marked necrobiosis of the

superficial layers with abundant leucocytes, chiefly polymorphonuclear in nature, and varying bacterial infiltration.

In postabortal peritonitis the peritoneal cavity usually contains a large amount of more or less turbid purulent fluid. The intestines are distended and reddened. In rapidly fatal cases, several liters of exudate may be found without evidence of localization of the infection. More often, pus pockets in various stages of organization occur in the lumbar gutters around the liver, in the cul-de-sac, and between the loops of small intestine. In late cases, very little free fluid may be present. A gelatinous exudate is spread throughout the peritoneum and causes the coils of intestine to adhere to each other. Localized pockets of pus may be found. The histologic findings are characteristic of purulent peritonitis and are without distinctive features.

How does the infection extend from the uterus to the peritoneum? In general, three modes of extension have been found: first, through the Fallopian tubes, second, through the parametrium, and third, through the myometrium.

1. *By Way of the Tubes.*—There has been considerable controversy as to whether or not fatal peritonitis can be conveyed from the uterus to the peritoneum by means of the tubes. Williams[2] stated, "In many autopsies I have seen upon women dead of puerperal infection, I have never seen one in which there was any evidence that infection occurred in this manner." Goodall[3] postulated that puerperal infection which extends by continuity of epithelial surfaces is gonorrheal in origin. Halban and Koehler,[4] in 69 cases of fatal puerperal peritonitis, found that spread of infection by way of the tubes alone occurred in twelve instances. Martland[5] studied 53 cases of postabortal peritonitis and found that the tubes were involved in thirty-nine.

In an epidemic of puerperal sepsis with peritonitis, Watson[6] states that the findings "point . . . . . to a primary lymphatic infection." Extension via the Fallopian tubes is said by him to be more common in postabortal than in postpartum infection.[7]

In the present series, by far the most common pathway of extension (66 per cent) of infection from the cavity of the uterus to the peritoneal cavity was through the tubes. In these cases, the tubes are swollen, red, and tortuous. Occasionally they may even appear gangrenous. The fimbriated ends of the tubes are frequently patent. In rare instances, the fimbriae may be glued together with the formation of a small pyosalpinx. When cut in cross section, an exudate identical with that in the peritoneal cavity is present, and the folds of the endosalpinx are inflamed, edematous, and occasionally gangrenous or hemorrhagic. Histologically there is an intense, acute bacterial endosalpingitis. The villae are thickened, edematous, and infiltrated with polymorphonuclear cells. Often the epithelium is desquamated. Pseudogland formation is absent. The muscle coats are infiltrated with leucocytes. Apparently as a result of the generalized peritonitis, the serosal surface of the tubes as well as of the parametrium and the myometrium are all extremely inflamed and edematous.

CASE 1.—F. M., an 18-year-old nullipara, complained of abdominal pain, fever, and vomiting following an induced abortion two days prior to admission, Dec. 9, 1933. Menses had always been regular and normal. The last menstrual period had started seven weeks before. Examination disclosed signs of generalized peritonitis, and she died six days after admission. At autopsy the abdomen contained 3,000 c.c. of creamy yellow pus. The endocervix and endometrium were entirely gangrenous and foul-smelling. The tubes were enlarged to three times their normal size and contained a considerable amount of pus. The fimbriated ends of the tubes were open. The endosalpinx was hemorrhagic. The appendix was normal. The myometrium, parametrium, and ovaries were normal. There was no thrombosis of the pelvic veins.

2. *By Way of the Parametrium.*—Extension of the infection from a suppurative endometritis through the parametrium to the peritoneum was found much less frequently in this series.

Infection of the pelvic cellular tissue is essentially of lymphatic origin. There can be no doubt that "by comparison with the nongravid uterus the lymphatic channels of the gestational uterus, although probably not numerically increased, are obviously tremendously enlarged in calibre."[8] Bacteria enter the lymph vessels from the infected endometrium

and produce lymphangitis and perilymphangitis. The surrounding connective tissue thereby becomes involved and an intense reaction occurs with leucocytic infiltration and much pouring out of serum so that the tissues become tense and edematous. (Parametritis or cellulitis of the broad ligaments.) A similar sequence may occasionally be observed as a result of infection originating in the open mouths of the venous sinuses of the endometrium. This causes thrombophlebitis and periphlebitis of the pelvic veins with extension to the cellular tissue of the parametrium. The gross and microscopic appearance of the lesion in cellulitis of the broad ligament associated with peritonitis is apparently identical with that of an uncomplicated parametritis, and has been described in detail elsewhere.[9] The exudate may be limited to the broad ligaments, or may extend anteriorly to the prevesical space, posteriorly to the perirectal space, or upwards to the retroperitoneal space.

The histologic appearance is characteristic of cellulitis, that is, edema, fibrin formation, and perilymphangitic and perivascular infiltration. The exudate is often mononuclear in nature but may be frankly purulent. It is particularly abundant about the infected lymphatic vessels and occasionally in and about the veins. The tubes and myometrium may appear to be normal except for inflammation of the peritoneal surface.

CASE 2.—M. F., a 27-year-old primipara, was admitted Aug. 19, 1932, because of lower abdominal pain, vaginal bleeding, chills and fever for two weeks following abortion. Induction was denied. Examination of the abdomen revealed extreme distention, tenderness, and rigidity. On vaginal examination, resistance in the fornices and cul-de-sac was noted. Death ensued eight days after admission. At autopsy there was a considerable amount of greenish-yellow fluid pus with fresh fibrin in the abdomen. The intestines were matted together and greatly distended. The uterus was slightly enlarged. The uterine mucosa was necrotic and gangrenous and contained a placental site on the posterior fundal wall. The tubes appeared normal and contained a scanty mucoid secretion. Both broad ligaments showed a marked cellulitis with edema of the areolar tissue extending to the pelvic walls. The uterine sinuses were thrombosed but the pelvic veins were not involved. The other organs showed cloudy swelling.

CASE 3.—E. A., a 19-year-old primipara, was admitted March 17, 1932, with the chief complaint of abdominal pain, vaginal bleeding, and fever following an abortion induced with a catheter eight days previously. She appeared critically ill with generalized peritonitis and died three days after admission. A blood culture was negative. At autopsy, 500 c.c. of brown watery fluid was found in the peritoneal cavity. This contained free-floating thick fibrinous plaques; similar plaques were attached to the serosa of the viscera. The uterus was enlarged to the size of a six weeks' pregnancy and was soft and boggy. On opening the uterine cavity, gangrene of the endometrium was present. The tubes did not appear enlarged or inflamed. The pelvic lymphatics were beaded and enlarged. The retroperitoneal tissues were inflamed and edematous.

The vast majority of postabortal parametric infections remain extraperitoneal. Extension occurs via the lymphatics and along the endopelvic fascial planes. Hofbauer[10] has shown that there is normally an increase in the number of wandering tissue cells (clasmatocytes, macrophages) in the parametrium during pregnancy and interprets this as a means Nature may use to limit the spread of infection.

The mode by which infection leaves the parametrium to enter the peritoneal cavity is not clear. If the peritoneum is merely an extended lymph space, as Goodall states, and "the pelvic peritoneum communicates by a thousand ostia with the lymphatics of the subperitoneal spaces," then the mechanism is clear. There are, however, several objections to this theory. First, the presence of peritoneal stomata has not yet been indisputably proved.[11] Second, according to anatomic studies by Rouvière[12] the lymphatics of the cervix and corpus are connected with each other and with those of the tube and ovary, and empty into the aortic, external iliac, and hypogastric nodes. No mention is made of a peritoneal anastomosis. Third, carcinoma of the cervix and body of the uterus metastasizes primarily through the lymphatics and by direct extension to the parametrium.[13] With further lymphatic extension the retroperitoneal nodes are affected, whereas the peritoneum is conspicuously free of metastatic involvement. The peritoneum may be implicated, not by lymphatic extension, but by direct invasion. It would seem, therefore, that a direct pathway of infection from the uterus through the lymphatics to the peritoneum has not been proved, although its possibility cannot be denied.

Halban and Koehler have stated that infection, whether of lymphatic or venous origin, may enter the general circulation and give rise to "metastatic" peritonitis. Watson and

Goodall have found that changes in the serous cavities, meningitis, pericarditis, pleurisy, and peritonitis, are more frequent with lymphatic than with venous spread. In the present series of cases, despite complete and careful autopsies, no evidence of infection has been seen in the serous cavities other than the peritoneum. There was not a single instance of pericarditis or pleurisy even though in several cases embolic lung abscesses were found associated with pelvic thrombophlebitis. Because of the absence of changes in the other serous cavities and the lack of evidence of diffuse embolization, transmission of the infection via the bloodstream does not seem adequately to explain the pathogenesis of postabortal peritonitis.

It is our belief that in these cases the infection reaches the peritoneum by direct bacterial extension from the parametrium or retroperitoneal tissues. Lymphangitis results in cellulitis, the overlying peritoneum becomes implicated, and eventually generalized peritonitis ensues by direct invasion. As might be expected, intermediate stages may be observed. In the majority of patients with pelvic cellulitis there is no evidence of a peritoneal involvement. In a somewhat smaller group, the peritoneum immediately overlying the inflamed broad ligament is edematous, swollen, and hyperemic, comprising the so-called "peritoneal edema of Polak."[14] Immunity factors, of which little as yet is known, probably further restrict extension to the overlying peritoneum. Occasionally, as a result of greater virulence of the invading organism or of a decreased local or general immunity, a generalized peritonitis does nevertheless result. Still more rarely, a parametrial abscess may rupture directly into the peritoneal cavity.

CASE 4.—E. S., a 24-year-old bipara who was two weeks overdue, complained of pain and bleeding following the insertion of a catheter eight days before admission. Since then she had had chills, fever, and persistent vomiting. Shortly before admission the patient collapsed. Examination of the patient on admission showed her to be in shock. The abdomen was distended but soft. Vaginal examination showed a hard tender mass in the left fornix which extended to the pelvic wall. The right fornix was shortened. There was considerable induration of the rectovaginal septum. The uterus seemed to be fixed in this exudate. Death occurred on the following day. At autopsy there was 2,500 c.c. of foul smelling thin pus in the abdomen. The endometrium and placental site were dark red, necrotic, and friable. Both the tubes and ovaries were normal. Bilateral parametrial abscesses were present, the left larger than the right. On section it was demonstrated that the right parametrial abscess had ruptured into the general peritoneal cavity.

In spite of the fact that in any large series of abortions studied clinically, parametritis is a more frequent complication than salpingitis, at necropsy fatal peritonitis will most often be found to be secondary to salpingitis. The parametrium tends to localize and restrict the infection and prevent its further spread to the peritoneum. On the other hand, virulent postabortal infection of the tubes, usually if not always, involves the peritoneum.[15]

3. *By Way of the Myometrium.*—Extension of infection from the endometrium to the peritoneum through the myometrium can be said to have occurred only if the tubes and parametrium appear normal and there is evident extension throughout the entire thickness of the uterine wall. This was the rarest method of infection encountered.

CASE 5.—C. M., a 21-year-old primipara, was admitted to the hospital Dec. 27, 1937, stating that after fourteen weeks of amenorrhea she had had a spontaneous abortion four days before admission, followed by lower abdominal pain, vaginal bleeding, and fever. On admission the temperature was 101° F., and the abdomen was soft and not distended. There was slight vaginal bleeding but no induration or masses in the fornices. Despite the administration of sulfanilamide, five days after admission the abdomen was distended, tender, and contained fluid. *Escherichia coli* was obtained on blood culture. Eleven days after admission indefinite masses were felt in the abdomen. Three days later, under local anesthesia, incision and drainage of the peritoneal cavity through bilateral McBurney incisions was done, and 1,000 c.c. of pus evacuated which was found on culture to contain *Esch. coli*. The patient died eight hours after operation. At autopsy there was an extensive purulent peritonitis with 1,500 c.c. of thick foul-smelling pus in the peritoneal cavity. There were multiple abscesses between the intestinal loops which were glued together by a plastic exudate and there was a large abscess underneath the liver. The uterus was somewhat enlarged, and the entire fundus was converted into a gangrenous plaque. The remainder of the endometrium was the seat of a suppurative endometritis without abscess formation. An extensive thrombophlebitis was present, involving the femoral, external iliac, hypogastric, vesical, uterovaginal, hemorrhoidal, common iliac, and renal veins. The inferior vena cava was normal. The para-

metrium, except for extensive thrombophlebitis, did not seem thickened. The tubes were normal in size and the lumina clean. The right lung had several small red infarcts and there was a thrombosis of the right pulmonary vein.

In this type of case the uterus, whole or in part, is converted into a suppurative or gangrenous plaque which on histologic study shows characteristic evidence of acute inflammation with fragmentation and necrosis of the myometrium. Although the possibility of direct emptying of the lymphatics of the uterus into the peritoneum cannot absolutely be denied, it would again seem that direct extension from the uterine musculature to the peritoneum is the most likely route of extension in this case. Occasionally a less severe suppurative process occurs and discrete abscesses are formed in the wall of the uterus varying from several millimeters to several centimeters in size, although it has been said that this lesion "is almost a curiosity." In all such cases suppurative endosalpingitis was also present and was probably the route of infection to the peritoneum.

CASE 6.—C. B., a 29-year-old primipara, stated that following six weeks of amenorrhea she spontaneously aborted two days prior to admission Nov. 8, 1938. She appeared acutely ill, with generalized peritonitis, and died four days after admission. Blood culture revealed 316 colonies of *Staphylococcus aureus* per cubic centimeter. At autopsy there was a marked plastic peritonitis throughout the general peritoneal cavity, most severe in the pelvis. The endometrium was necrotic, particularly at the placental site. The tubes showed suppurative endosalpingitis with pus in the lumina. The fimbriated ends were open. The uterus contained multiple small abscesses varying from a pinhead to a pea in size. The uterine and vaginal veins were thrombosed, although otherwise the parametrium was not thickened. There were coalescent multiple miliary abscesses of the lungs.

In addition to the pathologic changes already described, two other lesions are often encountered in association with postabortal peritonitis, namely, ovarian abscess and thrombophlebitis. An ovarian abscess may occur as a tubo-ovarian abscess or as a cortical abscess resulting from lymphatic extension to the center of the ovary,[12] or as an infection of a corpus luteum cyst by "spillage" of pus over the ovary from the peritoneum or the tube.

CASE 7.—P. J., a 17-year-old multipara, was admitted Oct. 6, 1936, with the following history: After six weeks of amenorrhea, turpentine was taken orally to induce menstruation. Five days before admission, severe lower abdominal pain, fever, vaginal bleeding, and passage of the products of conception had occurred. She had had chills for two days. The abdomen was tense, distended, and tender. On vaginal examination an indefinite soft mass with no circumferential induration was felt in each fornix. Despite intensive supportive therapy, the patient died nine days after admission. At autopsy, 2,500 c.c. of yellow, thick, foul-smelling pus was contained in the peritoneal cavity. The intestinal loops were matted together by dense adhesions. The uterus was normal in size, the endometrium gangrenous. On the right side a tubo-ovarian abscess measuring 3 by 2 by 2 cm. was found. The left tube was inflamed, thickened, and open at the fimbriated end. The mucosal lining of both tubes was gangrenous. The left ovary contained an infected corpus luteum cyst which measured 3 by 4 by 4 cm.

Thrombophlebitis of the uterine and ovarian veins is found frequently in postabortal peritonitis. It is believed that this lesion is usually secondary to infection of the parametrium or to direct extension from infected uterine sinuses. In the peritonitis cases it tends to remain localized in the pelvis and only rarely gives rise to pyogenic metastases. The reason for this is difficult to explain.

Discussion

In this series of 61 cases of postabortal peritonitis, all cases presented an endometritis of varying severity. The infection spread from the endometrium to the peritoneum as a result of direct extension through (1) the tubes, (2) the parametrium, (3) the myometrium, (4) by a combination of these routes. (Fig. 1.)

1. Direct extension through the tubes seemed to be the pathway of infection in 40, or 66 per cent, of the cases studied.

2. Extension of the infection from a parametritis to the peritoneum occurred in 6 cases, or 10 per cent. In one case the peritonitis was caused by a rupture of a broad ligament abscess into the peritoneal cavity.

3. The infection extended through the myometrium in 4, or 7 per cent, of the cases.

4. In 6 patients, endometritis, salpingitis, parametritis, and peritonitis were present. The pathway of infection was not clear.

5. In 4 patients, endometritis, abscess of the myometrium, salpingitis, and peritonitis occurred. It is probable that in this group the tubes were the chief pathways of extension as the myometrium contained discrete abscesses with no contiguous inflammation of the enveloping peritoneum. These cases are not included in the first group because of the questionable etiology of the peritonitis.

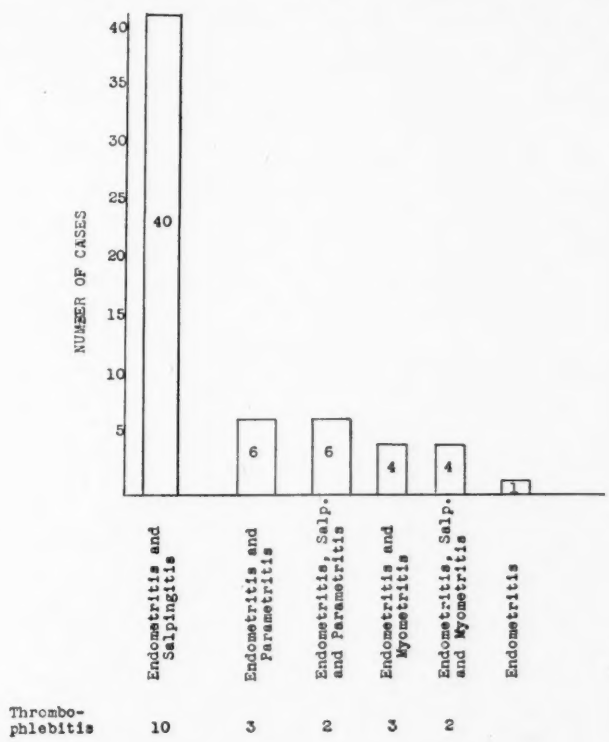

Fig. 1.—Pathogenesis of postabortal peritonitis.

Ovarian abscess was found 17 times, an incidence of 28 per cent, although no exact figure can be given as to the type of abscess present, since this data was not specifically recorded. It may occur with any mode of infection and was equally frequent with parametritis, salpingitis, or myometritis.

Thrombophlebitis of the uterine or ovarian veins, or of both, occurred in 20, or 33 per cent of all the patients observed. It was more common in the patients with parametritis or myometritis alone or in combination, than in those with salpingitis alone. Of 40 patients with salpingitis and peritonitis, 10 or one-fourth showed phlebitis, whereas in the 20 cases with parametritis, myometritis, and peritonitis, 10 showed venous inflammation. In 15 of the 20 patients there was localized thrombophlebitis. In 5, embolic abscesses of the lungs were present. No other sites of embolization were found despite careful study.

In this series the most common pathway of infection to the peritoneum was by direct extension through the tubes.

Summary

A series of 61 cases of postabortal peritonitis was studied.

The infection spread from the endometrium to the peritoneum by way of the tubes in 66 per cent, the parametrium in 10 per cent, the myometrium in 7 per cent, and in other combinations, 17 per cent.

References

1. Falk, H. C.: Am. J. Surg. **35**: 153, 1937.
2. Williams, J. W.: Bull. New York Acad. Med. **7**: 260, 1931.
3. Goodall, J. R.: Puerperal Infection, Montreal, 1932, Murray Printing Co., Ltd.
4. Halban, J., and Koehler, R.: Die pathologische Anatomie des Puerperal-processes, Vienna, 1919, W. Braumuller.
5. Martland, H. S.: Am. J. Surg. **26**: 90, 1934.
6. Watson, B. P.: Am. J. Obst. & Gynec. **16**: 157, 1928.
7. Watson, B. P.: Puerperal Sepsis and Thrombophlebitis, in Curtis: Obstetrics and Gynecology, Philadelphia, 1933, W. B. Saunders Co., Vol. II.
8. Wislacki, G. B., and Dempsey, E. W.: Anat. Rec. **75**: 341, 1939.
9. Falk, H. C.: Practical Clinical Gynecology, Am. J. Surg. **39**: 185, 1938.
10. Hofbauer, J.: Bull. Johns Hopkins Hosp. **38**: 255, 1936.
11. Hertzler, A. E.: Diseases of the Peritoneum, Philadelphia, 1930, W. B. Saunders Co.
12. Rouvière, H.: Anatomy of the Human Lymphatic System, Ann Arbor, 1938, Edwards Brothers, Inc.
13. Cullen, T. S.: Cancer of the Uterus, Philadelphia, 1909, W. B. Saunders Co.
14. Polak, J. O.: Pelvic Inflammation in Women, New York, 1931, D. Appleton-Century Co.
15. Frankel, O.: Personal communication.

STUDIES CONCERNING MORBIDITY AND MORTALITY FOLLOWING HYSTERECTOMY

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ALTHOUGH during the past decade a voluminous literature has accumulated concerning various problems associated with hysterectomy, comparatively few reports have been compiled with studies on morbidity and mortality. Presumably, one of the obstacles has been that we have no morbidity standard in gynecology which might permit uniform interpretation of the various factors. It is, therefore, of interest to investigate the incidence and etiology of morbidity and mortality in a gynecological clinic where the resident staff under supervision did 33 per cent of the operations. Furthermore, we believe that the publication of the findings will be of value to others for comparative study.

Materials and Methods

This study is based on a series of 980 consecutive hysterectomies performed during a twenty-six-month period, from Jan. 1, 1942, to Feb. 29, 1944. We had no particular reason for selecting this group other than to study the latest series over a two-year period and yet have a sufficient number. There were 643 complete, 253 subtotal, and 84 vaginal hysterectomies. These figures include both private and ward, white and Negro patients, operated upon by thirteen attending surgeons and sixteen members of the resident staff

TABLE I. TYPES OF HYSTERECTOMY AND OPERATORS

TYPE OF HYSTERECTOMY	VISITING SURGEON		RESIDENT STAFF		AVERAGE AGE (YEARS)	AVERAGE HOSPITAL DAYS	TOTAL NUMBER	PER CENT
	NUMBER	PER CENT	NUMBER	PER CENT				
Complete	435	67.4	208	32.6	43.6	13.1	643	65.6
Subtotal	185	73.1	68	26.9	40.7	13.3	253	25.8
Vaginal	50	59.5	34	40.5	53.9	16.3	84	8.6

(Table I). Operations performed by the latter were done under the supervision of an attending surgeon or the senior resident.

The indications for hysterectomy as well as the operative technique were uniformly followed by all. We made no attempt to grade the operative procedure according to the technical difficulties encountered in each case, since we observed that morbidity and mortality in this series did not depend on them. It was noted that after a very simple operation, a patient may suffer from hazardous complications, while after an extensive Wertheim procedure, another may have an uneventful convalescence. However, there is no doubt that over a long period of time and in an extensive series of cases technical difficulties do affect convalescence.

The interpretation of the various factors and the conclusion reached that the patient was morbid were based on an elevated temperature, rise in pulse rate, white cell counts, urinalysis, x-ray findings, and physical examination. No attempt was made to separate the white from Negro patients, as the latter comprised an insignificant number in this series. The postoperative course of these was not different from the white patients.

Pathologic and General Findings

Table II shows the pathology encountered in the series. It is of interest that 472 patients, or 48.1 per cent, were operated upon because of leiomyomas producing symptoms requiring surgical intervention. Among these, 120 were complicated by bilateral chronic salpingo-oophoritis. Twelve per cent, or 118 patients, were operated upon for chronic bilateral salpingo-oophoritis. Procidentia was present in 115 patients or 11.7 per cent. Vaginal hysterectomy was done in 84 of this group, and none of these was complicated by other pelvic pathology except cystocele, rectocele, or both. The miscellaneous group includes patients with functional flowing and endometrial hyperplasia, chronic cervicitis with hypertrophy, badly lacerated cervix with persistent vaginal discharge, and chronic endometritis and myometritis. These accounted for 68 operations or 6.9 per cent of the series. Various degrees of adenomyosis was found on microscopic examination in 197 patients or 20 per cent. Malignancy of the cervix, endometrium, or ovaries was present in 79 cases or 8 per cent. Of these, 49 had adenocarcinoma of the endometrium, ten of which, or 20.4 per cent, were complicated by leiomyomas. Although tuberculous salpingitis has an incidence of about 5 per cent of all inflammatory processes of the tubes (Curtis, 1942),[1] only 9 cases or 0.9 per cent were found in this group. If we had calculated the percentage on the basis of the number of patients examined to find these, it would be insignificantly small, as in all the

TABLE II. PATHOLOGY PRESENT

PATHOLOGY	HYSTERECTOMY		
	COMPLETE	SUPRAVAGINAL	VAGINAL
Leiomyomas	333	139	0
Chronic salpingo-oophoritis	77	41	0
Miscellaneous	51	17	0
Adenocarcinoma of the endometrium	49	0	0
Procidentia	29	2	84
Benign ovarian growths	23	10	0
Endometriosis (pelvic)	21	25	0
Carcinoma of the cervix	16	0	0
Endometrial polyps	16	8	0
Chronic endometritis	14	1	0
Tuberculous endometritis and salpingitis	7	2	0
Other malignancies of the uterus	4	1	0
Carcinoma of ovaries	2	7	0
Bicornute uterus	1	0	0
Total	643	253	84

patients except one the diagnosis was made before operation in the sterility clinic on the basis of tuberculous endometritis.

Table III lists the number of patients who had had previous abdominal operations and the additional procedures carried out along with hysterectomy. Most of the previous operations had been on the pelvic organs, but some had been cholecystectomies, appendectomies, and bowel operations. There was no increase in morbidity in patients who had had previous operations. In some, extensive omental and bowel adhesions were present which made the hysterectomy more difficult, but did not excessively prolong the procedure. Previous ventral uterine fixations, Caesarean sections, and suspensions presented no problem. In fact, we have the distinct impression that patients who have had previous abdominal operations do as well or better than fresh cases.

TABLE III. PREVIOUS OPERATION AND OTHER PROCEDURES WITH HYSTERECTOMY

PROCEDURES	HYSTERECTOMY					
	COMPLETE		SUPRAVAGINAL		VAGINAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Previous abdominal operations	253	39.3	102	40.3	10	11.9
Salpingo-oophorectomy	629	97.6	250	98.4	0	0
Vaginal plastic	73	11.3	12	4.7	77	91.6
Appendectomy	376	58.4	116	45.8	0	0

Bilateral or unilateral salpingo-oophorectomy was done in 629 patients or 97.6 per cent of those undergoing complete hysterectomy, and in 250 patients or 98.4 per cent of those undergoing the supravaginal operation. It has been a general rule in this clinic to remove both ovaries and tubes in patients over 45 years of age, if hysterectomy were indicated. This procedure was followed in most of the patients with chronic pelvic inflammation, regardless of age, if the uterus were removed. This presumably has avoided occasional secondary operation, since cyst formation in the remaining ovary occurs in patients who have had chronic pelvic inflammation.

Anterior colporrhaphy, colpoperineorrhaphy, or both, were done on 73, or 11.3 per cent, of those having complete hysterectomies, and on 12, or 4.7 per cent, of those having subtotal operations. These procedures were done on 77, or 91.6 per cent, of the vaginal hysterectomy group. These additional operations did not increase the morbidity in the complete and subtotal hysterectomy groups, but in the vaginal hysterectomy series, it was noted that the more extensive the plastic operation, the more frequent were the complications. This was particularly striking in patients with large rectocele and enterocele which are commonly present with procidentia.

Appendectomy was done routinely in all abdominal operations, except in a rare case, where the appendix was grossly normal, obviously atrophied, difficult to expose, or could not be removed without excessively prolonging the operation. Phenol-alcohol or cautery technique was used routinely. The appendiceal stump was left exposed in most; in some it was buried with a figure-of-eight suture. Appendectomy did not influence the morbidity in this series. It is interesting that in 152, or 30.9 per cent, of the routine appendectomies, the appendix was found on microscopic examination to be chronically inflamed, and possibly a potential menace.

Causes of Morbidity

Table IV shows the causes of morbidity which were established as etiology of elevated temperature and rise in pulse rate in three types of hysterectomy. Pelvic peritonitis and parametritis were responsible for almost half of the morbidity in the vaginal hysterectomy group, and occurred more frequently in the subtotal than in the complete hysterectomy series. Extensive plastic procedures with vaginal hysterectomy and opening of the peritoneal cavity in a contaminated field were likely responsible. In septic cases, ineffective drainage through the narrow lumen of the remaining cervix in supravaginal hysterectomy patients contributed to extension of sepsis and prolonged elevated temperature. If sepsis should occur in those who had complete hysterectomy, ample room is provided by the wide vaginal cuff for immediate drainage and localization of the process. Cauterization of the cervix, too, creates a nidus of necrotic tissue ideal for the origin of sepsis. In this series pelvic peritonitis and parametritis occurred three times as often in the subtotal as in the complete hysterectomy group.

There were no bladder, ureteral, or bowel injuries in the entire series. Cystitis occurred more often after the subtotal hysterectomy, but its incidence in the entire series was remarkably low. Pyelitis, too, was rare. The administration of sulfonamides rou-

TABLE IV. CAUSES OF MORBIDITY

COMPLICATION	HYSTERECTOMY					
	COMPLETE		SUPRAVAGINAL		VAGINAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Femoral phlebitis	12	1.8	3	1.1	0	0
Cystitis	9	1.4	4	1.5	2	2.3
Abdominal wound sepsis	8	1.2	7	2.7	0	0
Pelvic peritonitis	6	0.9	7	2.7	38	45.2
Postoperative hemorrhage (vaginal)	5	0.7	0	0	2	2.3
Lobar pneumonia	4	0.6	0	0	0	0
Pulmonary atelectasis	4	0.6	2	0.7	0	0
Hematoma of wound	3	0.4	2	0.7	0	0
Pulmonary infarct	3	0.4	1	0.3	0	0
Psychosis	3	0.4	0	0	1	1.1
Superficial phlebitis	3	0.4	2	0.7	0	0
Pyelitis	2	0.3	0	0	0	0
Mechanical intestinal obstruction	1	0.1	0	0	1	1.1
Paralytic ileus	0	0	0	0	1	1.1
Atypical pneumonia	1	0.1	0	0	0	0
Unknown	122	19.8	53	20.9	0	0

tinely to all patients with inlying urethral catheters, undoubtedly had a prophylactic effect. On the other hand, deep femoral phlebitis was noted more often after complete hysterectomy. It occurred in 12 patients, or 1.8 per cent. Only 3 patients, or 1.1 per cent, of the subtotal group developed this complication. Likewise, postoperative hemorrhage occurred in 5 patients, or 0.7 per cent, undergoing complete hysterectomy, but none in those who had the subtotal operation.

The remainder of Table IV shows a small number of various complications from which nothing definite can be drawn, except that they do occur incidentally with other abdominal operations. However, there were 122 patients, or 19.8 per cent, of the complete, and 53 patients, or 20.9 per cent, of the subtotal hysterectomy groups, who had an elevated temperature and pulse rate for the first two to four days postoperatively, but whose hospital stay was not prolonged and the temperature and pulse were normal on the usual day of discharge from the hospital. We could not find any cause for the elevated temperature and pulse. Minimal pulmonary atelectasis and low-grade pelvic sepsis, which could not be recognized clinically, might possibly have been the cause. This group presents a challenge to any morbidity standard which one might establish for hysterectomy.

Mortality

Table V lists the causes and incidence of mortality. No deaths occurred in the subtotal hysterectomy group. There were three deaths in the complete, and one in the vaginal hysterectomy group, respectively. This gives complete hysterectomy a mortality rate of 0.46 per cent and vaginal hysterectomy a rate of 1.1 per cent. The rate for the entire series is 0.40 per cent.

Two deaths occurring after complete hysterectomy were in debilitated patients with advanced adenocarcinoma of the fundus, and one was in a young patient with pelvic endometriosis who developed postoperative hemorrhage and peritonitis. Of the four deaths occurring in this series, three were in patients operated upon by the visiting surgeons, and one by the resident staff (Table V).

TABLE V. MORTALITY

PATIENT NUMBER	AGE	PATHOLOGY	CAUSE	OPERATOR
Complete Hysterectomy—3 Deaths			*Mortality Rate—0.46 Per Cent*	
1	69	Adenocarcinoma of the fundus	Lobar pneumonia and paralytic ileus	Staff surgeon
2	68	Adenocarcinoma of the fundus	Acute coronary occlusion	Staff surgeon
3	35	Pelvic endometriosis	Hemorrhage and peritonitis	Staff surgeon
Vaginal Hysterectomy—1 Death			*Mortality Rate—1.1 Per Cent*	
1	38	Procidentia	Hemorrhage and peritonitis	Asst. resident

Discussion

The review of the literature on morbidity after hysterectomy reveals that many factors are involved and that no morbidity standard is suitable for this operation. Some authors (Danforth, 1943,[2] Jones and Doyle, 1943[3]) used the obstetric standard, but found it inadequate. We also find that it is difficult to apply any standard which could be used by all for a comparative study. In a study of any series of operations, it may be readily seen that a variety of complications may arise which are not inherent in the procedure but may be the sequelae of the simplest operation. It is difficult to define prerequisites as to what constitutes morbidity in a given patient. Numerous factors are involved. Some complications depend on the individual patient; her age, pathology encountered, and diseases remote from the surgical procedure. Others may depend on the ability and experience of the surgeon as well as on the procedure he chooses (Bartlett and Simmons, 1932,[4] Dupertius and Zollinger, 1938,[5] Smith, 1940[6]). We believe, however, that much may be accomplished if the incidence of various complications is reported by a large number of observers from several clinics. From comparative studies of these reports certain generalizations might be formed and attention focused upon the etiology of morbidity and its incidence reduced.

In this study we made every effort to account for each complication and, therefore, reviewed all the factors pertaining to the individual case. It was noted that in this series deep femoral phlebitis occurred only in patients over 35 years of age, and was also more frequent after complete hysterectomy. Age also was noted to influence the incidence of morbidity which was more frequent in those over 45 years. Operations on patients with benign chronic pathologic conditions were followed by a low incidence of morbidity, but patients with malignant growths of the uterus or the adnexa suffered from frequent complications. Two of the four deaths in this series were in patients with adenocarcinoma of the endometrium. To be sure, both were over 65 years of age and poor risks, but others in this age group with benign conditions tolerated similar procedures well. Abdominal wound sepsis and poor healing of tissues are frequent with malignancies.

Although it is not the purpose of this paper to enter into the much discussed question of whether complete or subtotal hysterectomy should be done routinely, we are in complete agreement with other observers (Bryan and Traube, 1936,[7] Masson, 1927[8] and 1940,[9] McKibbon and Counsellor, 1942[10]) that complete hysterectomy is by far the better procedure. The main advantage of the total operation is that the cervix, as the possible future site of infection or malignancy, is removed, and conization or cauterization is hardly of any value as compared with complete removal. We have not noted any shortening or prolapse of the vagina following a complete hysterectomy, neither have the patients complained of a dry vagina as in contrast to complaints of leucorrhea after the subtotal operation. In this series, 65.6 per cent were complete, 25.8 per cent were subtotal, and 8.6 per cent were vaginal hysterectomies respectively. Postoperative complications were present in 9.9 per cent of the complete, 11 per cent of the subtotal, and 53.1 per cent of the vaginal hysterectomies.

The average hospital stay was 13.1 days for the complete, 13.3 days for the subtotal, and 16.3 days for the vaginal hysterectomy.

It is of interest that the highest morbidity and mortality and the longest hospitalization were in the vaginal hysterectomy group. Undoubtedly, this

was due to the extensive plastic procedures and opening of the peritoneum which routinely accompanied the operation, for all these patients had procidentia with cystocele, rectocele, and enterocele. Also the average age of these was 53.9 years in comparison with an average of 43.6 years for the complete, and 40.7 years for the subtotal hysterectomy patients. Danforth, 1943,[2] reported a series of 517 consecutive vaginal hysterectomies with a morbidity rate of 42.1 per cent. There was no mortality. Masson, 1940,[9] reported 607 cases from the Mayo Clinic over a five-year period with a mortality rate of 1.5 per cent. However, the morbidity was not reported, but in an earlier paper (Masson, 1937[11]) he states that, after vaginal hysterectomy, patients averaged 18.4 hospital days, in contrast to 16.5 days for those who had an abdominal total hysterectomy. In this series the morbidity rate of the vaginal hysterectomy was 53.1 per cent and the mortality rate 1.1 per cent, both exceeding those after the abdominal operation. The late results were also inferior to the combined abdominal and plastic procedure for procidentia. Although the end results were satisfactory for this age group, the vagina was markedly shortened in 15 patients or 17.8 per cent; one developed complete prolapse of the vagina; and 16 patients, or 19 per cent, had recurrent cystocele or enterocele. However, secondary plastic operations were performed on the latter without morbidity or mortality. The results in this small group are not intended to condemn the procedure, which has its indications, but, with limitation.

One-third of all the operations in this series was done by the resident staff under the supervision of the visiting surgeon or the senior resident. It is of interest that only one death occurred in this group (Table V). To be sure, these patients were selected, and the visiting surgeons operated upon all the poor risk cases, but this did not exclude the operations which were technically difficult to perform.

Summary

1. A study of the causes of morbidity and mortality in 980 patients following hysterectomy is presented.

2. The morbidity rate for the supravaginal hysterectomy was higher than that for the total hysterectomy; and for the vaginal operation it was 53.1 per cent.

3. The incidence of cystitis and pyelitis has been reduced to 3 per cent by the prophylactic use of sulfonamides.

4. The mortality rate for the entire series was 0.4 per cent.

5. The resident staff under supervision performed 33 per cent of the operations with a mortality rate of 0.32 per cent.

References

1. Curtis, A. H.: A Textbook of Gynecology, ed. 4, Philadelphia, 1942, W. B. Saunders Co., p. 217.
2. Danforth, W. C.: Surg., Gynec. & Obst. **76**: 411, 1943.
3. Jones, H. O., and Doyle, L. W.: Am. J. Obst. & Gynec. **46**: 60, 1943.
4. Bartlett, M. K., and Simmons, R. A.: Surg., Gynec. & Obst. **55**: 777, 1932.
5. Dupertius, S. M., and Zollinger, R.: Surg., Gynec. & Obst. **67**: 689, 1938.
6. Smith, P. H.: Am. J. Obst. & Gynec. **40**: 118, 1940.
7. Bryan, W. A., and Traube, C. C.: Ann. Surg. **103**: 914, 1936.
8. Masson, J. C.: Am. J. Obst. & Gynec. **14**: 486, 1927.
9. Masson, J. C.: Am. J. Obst. & Gynec. **48**: 255, 1940.
10. McKinnon, D. A., and Counsellor, V. S.: Surg., Gynec. & Obst. **74**: 957, 1942.
11. Masson, J. C.: S. Clin. North America **17**: 1131, 1937.

FIVE YEARS' EXPERIENCE WITH CAUDAL ANESTHESIA IN PRIVATE OBSTETRIC PRACTICE

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IN JULY, 1944, in a published commentary,[1] I called attention to the fact that the administration of an anesthetic agent into the caudal canal is never risk free. I indicated that the use of an indwelling needle or catheter in the caudal canal increases the possible complications, and, more particularly, I attempted to point out that caudal anesthesia has an inherent tendency to arrest the progress of normal labor. Thus, even though the risk of caudal anesthesia may be minimized to the point of negligibility, its administration before the terminal stage of labor constitutes unsound obstetrics. These conclusions were based on a reasonably broad experience with caudal anesthesia in a large obstetric clinic during the years 1938 and 1939.[2]

Following the publication of the commentary I received a large number of personal communications from obstetricians throughout the country. These letters were expressions of men who shared my conviction that the propagandists who were promoting continuous caudal analgesia were advocating unsound, unsafe obstetrics. The great majority of these personal communications contained an inquiry concerning my opinion of single injection, terminal caudal anesthesia, and asked if and when I use it. This present report concerns my experience with single injection, terminal caudal anesthesia for delivery during the five years that I have been in private practice. Most of this practice is done in the Washington County Hospital, Hagerstown, Maryland, an institution of about 175-bed capacity, where there are no resident house officers and no service cases. A small part of the practice is done as consultations in several smaller hospitals in surrounding counties. Under such circumstances any procedure used in private obstetric practice must be not only safe but simple and free from complications.

Practically all primigravidas are delivered by elective outlet forceps with median perineotomy and repair. Many multiparas are delivered by outlet forceps with or without perineotomy, as indicated. Such a routine calls for some type of anesthesia for delivery and repair. Since there are no house physicians, any general anesthetic must be administered by a private medical practitioner or a general duty graduate nurse, untrained in anesthesia. For the past five years I have used single injection caudal anesthesia for delivery and repair in selected cases, and over this period of time I have used it with increasing frequency. During the past several years the local doctor shortage has made it necessary to depend upon an anesthetic procedure which can be carried out by oneself. This fact, plus the fact that the procedure, in my hands, has been completely satisfactory, free from complications and enthusiastically received by the patients, accounts for my increasingly frequent use of terminal caudal anesthesia. However, I do not attempt to use the procedure in every patient delivered. Some patients are psychologically unsuited for regional anesthesia; in others, labor progresses so rapidly that the procedure is unnecessary and impracticable; in others, there is sufficient subcutaneous fat over the sacrum to prevent identification of the sacral hiatus by palpation and the procedure is not attempted. If caudal anesthesia is at-

tempted, and the needle does not definitely enter the sacral canal, no fluid is injected. This fact can be verified by a sign which I reported in 1939;[2] that is, the tip of the needle can be felt to impinge on the anterior surface of the posterior sacral wall after it has entered the sacral canal.

My records reveal that in the five years from August, 1939, to August, 1944, 318 obstetric cases have been delivered under caudal anesthesia and seen for the routine six weeks' postpartum checkup examination. Forty-five of the total represent obstetric complications such as breech presentations, transverse arrests, etc., in which procedures other than outlet forceps deliveries were done. Many of these were seen in consultation. In every case but one, anesthesia was excellent and no supplementary anesthetic was required. In one case (occiput directly posterior and prolonged, arrested second stage) unilateral anesthesia only was obtained and inhalation anesthesia was necessary. One cesarean section was done in this group of 45 with no supplementary anesthesia necessary. However, in my opinion, caudal anesthesia for cesarean section is hazardous because the solution must be driven higher than usual to get a satisfactory anesthesia and this carries an increased risk of vascular collapse.

The remaining 273 cases represent normal obstetric patients who were delivered under caudal anesthesia by elective outlet forceps. The group represents only 243 individuals, as 30 patients were delivered in consecutive pregnancies. Two hundred ten of this group were primigravidas and perineotomy was done in every one. Thirty of the multiparas had perineotomy. In this elective outlet forceps group, supplementary anesthesia was necessary in only one case, which developed unilateral anesthesia only. In this case, local infiltration anesthesia was used on the unanesthetized side.

This total group of 318 cases, in which caudal anesthesia was entirely satisfactory in 316, represents an attempt to administer caudal anesthesia to 320 cases. In two attempted cases the caudal canal could not be entered although it seemed clearly palpable. No solution was injected in these two cases.

In the total group of 318 cases there was no maternal mortality and no complication from the anesthetic, either maternal or fetal. One stillborn fetus was delivered by breech extraction after a prolonged second-stage labor, the baby having died in utero before the patient was seen in consultation. One other baby died four days post partum from erythroblastosis. All other babies were born in excellent condition. Caudal anesthesia is a tremendous advantage to the prematurely delivered infant.

In the first 145 cases in this series, 1 per cent novocain was used as the anesthetic agent, and in the last 173 cases 1.5 per cent metycaine was used. I prefer metycaine because of its rapid and prolonged action. Thirty cubic centimeters of metycaine solution will usually produce complete caudal anesthesia for one hour. Its action may be prolonged by the addition of adrenalin but more prolonged action is not necessary for the usual delivery and repair. Metycaine may produce a very mild general systemic reaction which patients describe as lightheadedness and generalized tingling. Vomiting occasionally occurs if the solution is injected too rapidly. These reactions, if they occur, are fleeting and are often followed by a mild euphoria when patients frequently say, "I feel wonderful."

Technique

The technique used today is slightly modified from that advocated in 1939.[2] The modifications are pointed toward safety and comfort during administration. No special

equipment is necessary. The sterile pack contains one each of the following: small towel; 3 inch, 19 gauge spinal puncture needle; small hypodermic needle; 10 c.c. syringe; 150 c.c. Pyrex basin; ampule containing 5 c.c. of 20 per cent metycaine with file for opening; and several gauze sponges.

The sterile pack is opened on a utility table and the operator dons sterile gloves. The 20 per cent metycaine is transferred from the ampule to the Pyrex basin and the utility nurse dilutes this with 60 c.c. of sterile normal saline solution (the flasks of saline contain this measured amount before autoclaving). The resulting mixture represents 1.5 per cent metycaine solution. While the operator is mixing the solution, the nurse cleans a wide area of skin overlying the sacral hiatus with iodine followed by alcohol. During this skin sterilization, the patient (now in hard labor) lies on her left side with the knees flexed. With the patient still on her side, the operator infiltrates the skin and subcutaneous tissue overlying the hiatus with several cubic centimeters of metycaine solution, using the 10 c.c. syringe and hypodermic needle. The skin weal is pressed away with the finger. Following the next painful uterine contraction the patient is placed in the knee-elbow position with the back horizontal, and the towel is placed over the patient's back so that the operator can palpate the midline of the back through the towel. This maneuver helps considerably in directing the needle into the sacral canal. The exact location of the hiatus is identified, and the 19 gauge needle with stylet is inserted through the hiatus into the canal. The needle is then introduced almost up to the hub. During this penetration it is important to keep the direction in the midline and it is also important to moderately depress the hub of the needle so that the tip of the needle travels close to the anterior surface of the posterior sacral wall. When the needle has penetrated to most of its length, its tip will meet the curving sacral wall and can be felt to impinge against it. This sign definitely verifies the presence of the needle in the caudal canal. Keeping the tip of the needle close to the posterior sacral wall also acts as a safeguard against the accidental penetration of a low-lying dural sac. The stylet is then removed, the 10 c.c. syringe attached to the needle and the plunger withdrawn. If spinal fluid is withdrawn, the procedure is abandoned. This happened twice in my early experience with caudal anesthesia but it has not happened since I have been careful to keep the needle close to the posterior sacral wall. Frequently a drop or two of blood will be aspirated into the syringe but this may be safely ignored so long as there is no steady flow indicating that the needle lies intravascular. The syringe is then removed and filled with 10 c.c. of metycaine solution which is injected slowly through the needle under only moderate pressure. The patient is kept in the knee-elbow position to this point in the procedure. The syringe is now detached from the needle and the patient placed on her left side again with the knees flexed and the needle remaining in the caudal canal. Several minutes are allowed to elapse during which time the nurse constantly palpates the radial artery and checks the patient's pulse. Any accident from the injection will be manifested first by a rapid, weakening pulse. So long as the pulse remains normal, one may feel sure there are no complications and it is absolutely necessary to impress this fact upon every delivery room nurse. After several minutes observation the patient is requested to move her toes. If she can move her toes and there is no sensation of numbness, another 10 c.c. of metycaine are injected after aspiration reveals no fluid. The patient should feel no sensory changes in the feet several minutes after the first 10 c.c. have been introduced. If she does, it is wise to defer the second 10 c.c. and look for motor weakness in the legs, which would suggest intradural injection although this would be very unlikely after the previous precautions. However, it is advisable to be overcautious with caudal anesthesia. Several more minutes are allowed to elapse after the second injection, when a third 10 c.c. are injected after a negative aspiration test. Following this final 10 c.c. injection, the needle is immediately withdrawn and the patient placed flat on her back. The patient has been having painful uterine contractions during the administration but by the time she is turned on her back the pains are somewhat dull. She is usually conscious of one or two contractions after being placed on her back but this discomfort is usually confined to a small area immediately above the symphysis pubis. Contractions continue thereafter painlessly and typical caudal anesthesia develops completely, ten minutes or so following relief from contraction pain. Anesthesia lasts approximately one hour, which is more than enough time to drape the patient and carry out the delivery and repair.

Many patients may be kept on their side for the insertion of the needle and the injection of the entire 30 c.c. of solution, but I prefer the knee-elbow position for the initial part of the procedure for two reasons: First, I find it easier to insert the needle properly and quickly in this position. Second, I think unilateral anesthesia is less likely

to develop if the first 10 c.c. are injected in the knee-elbow position. To the uninitiated it will seem an awkward position for the patient, but the fact is that the needle insertion and the original injection can usually be accomplished between two contractions so that the patient experiences no discomfort while in this position.

Time of Administration

Although a few multiparas and the occasional primigravida may be delivered spontaneously under caudal anesthesia, its field of greatest usefulness is that of operative delivery. The practice of elective outlet forceps delivery with perineotomy is not endorsed by all obstetricians but the defense of such a routine is beyond the scope of this communication. However, it must be emphasized that the obstetrician who does not do elective forceps deliveries cannot use caudal anesthesia. The self-styled specialist who practices on the fringe of the specialty should not do elective forceps or use caudal anesthesia. If he does, both he and his patients will, soon or later, regret it.

Most of my patients are given a combination of heroin and hyoscine, hypodermically, as an analgesic before the terminal stage of labor is reached. In general, when the head has reached the perineal floor and the cervix is fully dilated, the caudal anesthesia is administered. In certain cases the anesthetic may be given before this stage is reached. Under certain conditions caudal anesthesia will markedly accelerate the latter part of the first stage of labor. If the patient is in hard labor and the head is deep in the pelvis, if the cervix is at least 5 cm. dilated and thin and if the membranes are ruptured, the cervix will often disappear and retract within a few minutes after the administration of caudal anesthesia. It is absolutely essential that the above conditions be present before caudal anesthesia can be expected to bring about this rapid cervical dilatation and completion of descent. When caudal anesthesia is administered in one 30 c.c. dose, as described above, to a patient in which the conditions just enumerated are present, her total labor is definitely shortened. I frequently use caudal anesthesia under these conditions with very gratifying results, particularly in multiparas. This practice must not be confused with the practice of administering caudal anesthesia promiscuously under any circumstances or at any stage of labor, primarily to relieve the pains of labor, as advocated by the promoters of continuous caudal analgesia.

Conclusions

The advantages, risks, and limitations of caudal anesthesia in obstetrics were pointed out in 1939.[2] Since that report, the advantages of the principle have been widely publicized in both scientific and lay journals so that there is no need to resummarize them. Unfortunately, the "moonshees,"* in their recent prolific publications, have either failed to recognize or failed to divulge the limitations of the principle. Such uncritical, overenthusiastic reporting naturally met with resentment in the trained and sage obstetric world. However, it must be recognized that under certain conditions caudal anesthesia is useful and should be an integral part of the armamentarium of the obstetrician who knows when to use it and when not to use it.

The employment of any procedure in private practice without trained assistance is an accurate criterion of its practicability. The present report reveals my experience with terminal caudal anesthesia attempted in 320 cases. In two cases administration was abandoned because the caudal space could not be penetrated. In two other cases supplementary anesthesia was necessary. In the 316 cases remaining, the procedure was completely satisfactory with no maternal or fetal complications. This series does not represent my initial experience with caudal anesthesia. In my earlier experience the percentage of failures was significantly higher, indicating that the administration is technically difficult and that practice and experience are essential for satisfactory results. However, I know that any other obstetrician can attain the same

*See Webster's New International Dictionary, Second Edition.

gratifying results. The only requisites are that he have patience and that he be a trained obstetrician. The obstetrician can master the technique of caudal anesthesia in a comparatively short time, but the anesthetist cannot become an obstetrician in that same short time.

References

1. Baptisti, A., Jr.: Am. J. Obst. & Gynec. 48: 103, 1944.
2. Baptisti, A., Jr.: Am. J. Obst. & Gynec. 38: 642, 1939.

A QUADRIOVULAR QUADRUPLET PREGNANCY*

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THE exact incidence of quadruplet pregnancy is variously stated according to the method adopted in trying to arrive at it. Heslin suggested that it is determined by the following ratio: twins occur 1 in 80 births, triplets 1 in 80^2 (which is one in 6400 births), and quadruplets 1 in 80^3 (which is one in 522,000 births).

In a five-year period, 1924 to 1928, Hernstein and Pflatz found a ratio of 1 in 783,041 births in Germany. The Statistical Bulletin of the Metropolitan Life Insurance Company for May, 1944, quotes figures which show that the incidence of quadruplet births in the United States for the years 1933 to 1941 inclusive was 1 in 502,230 births. I am informed by Mr. Duffield, Director, Bureau of Records and Statistics, that there is no record of the birth of quadruplets in New York City prior to the present one. Their occurrence is thus of sufficient rarity as to justify the presentation of an individual case.

The Mother.—The mother was first seen by me in June, 1943. She was then 27 years of age; she had one child, a boy, 5½ years of age. She had had one other pregnancy which ended in early abortion in 1941. There was no febrile reaction following this but she had not felt well since. Her principal complaint was more or less constant pain in the lower abdomen, which became greatly aggravated ten or twelve days following menstruation. This pain continued until the onset of the next period, at which time it became still more severe and was present on both sides. The pain was so incapacitating that she could not continue her occupation as a dancer and was forced to stay in bed for the first two days of menstruation. The menstrual periods occurred regularly every twenty-four days and lasted for five or six days.

There was no history of multiple births in her family.

In general physique the patient was 5 feet 5 inches in height, small and slender, weighing 118 pounds. General examination of cardiac, respiratory, and excretory systems was entirely negative. Pelvic examination revealed a good pelvic floor, deep vagina, parous, noncatarrhal cervix, directed downward and backward. The uterus was anteverted, freely mobile, slightly above average in size, and rather firm in consistence. Both ovaries were easily palpable, freely mobile, firm in consistence, not enlarged but more sensitive than usual. No nodulation suggestive of endometriosis could be felt through any of the vaginal fornices.

Patient had consulted several doctors for relief of her pain and had been treated with all sorts of sedatives and practically every known hormone without benefit.

After seeing and examining her I made the following note: "It is difficult to account for the pain unless on the basis of sclerosis of the ovaries, affecting ovulation and corpus lutuem formation, or, possibly, of adenomyosis of the uterus. The only operative treatment one could suggest would be presacral sympathectomy or possibly hysterectomy. Advised against either of these until she has given herself the chance of at least one more pregnancy." It is interesting to note that in the six months following the delivery

*Presented before the New York Obstetrical Society, Nov. 14, 1944.

of the quadruplets the patient has experienced the same type of pain, though in much lesser degree. It now diminishes as menstruation approaches and is only slight during the actual period. Is it possible that this pain, beginning at the time of ovulation, is indicative of the ripening and rupture of multiple follicles and its continuation to the formation of multiple corpora lutea with the threat, or hope, of further multiple pregnancies if opportunity offers?

In any case, the patient took my advice for, on Nov. 2, 1943, she reported that her last menstrual period had been on July 24 and that she was pregnant.

The Pregnancy.—Last menstrual period began July 24, 1943, and the calculated date of delivery was April 31, 1944. The actual date of delivery was March 29, 1944.

When seen on November 2, which was fourteen and one-half weeks after her last menstruation, she gave a history of having had slight spotting of blood at the fifth week and intermittent brownish discharge until the middle of October. She had had intermittent abdominal pain for the past two months.

Examination showed a soft, rounded, fluctuant swelling reaching to the umbilicus. No fetal heart sounds could be heard; no ballottement could be elicited. The cervix was soft and situated high in the pelvis.

On November 8, when she was just over fifteen weeks pregnant, my note was as follows: "Uterus to above umbilicus; evidently contains a great deal of fluid as it is quite fluctuant. Uterine souffle is heard but no fetal heart sounds. No ballottement obtained. There is certainly hydramnios and probably a multiple pregnancy."

On November 19 her weight was 133 pounds. Blood pressure was 110/70. The uterus rose to halfway between umbilicus and ensiform cartilage, and she was very uncomfortable.

The enlargement and discomfort increased, making it difficult for her to attend to her household duties, so on December 7 she was admitted to the hospital to rest for a few days. She was then four and one-half months pregnant and the abdomen was as large as with a normal term pregnancy. An x-ray taken at this time showed "the skeletal structures of at least four feti" (Figs. 1 and 2). Fetal heart sounds could now be heard.

She returned home but had to rest a great deal. She had occasional feelings of faintness when on her feet, and the intermittent abdominal pain continued. Her discomfort ultimately became so great that she was admitted to the hospital on January 29 for complete bed rest. The pregnancy was then in its twenty-seventh week. It was noted that she was dyspneic and tired; there was mild ankle edema, no hypertension. Four fetal hearts could be heard on auscultating over the four quadrants of the abdomen. From then on she was continuously confined to bed until she went into labor on March 29, 1944, which was thirty-five and one-half weeks from the time of her last menstrual period.

To the foregoing a few more details may be added. Her weight increased from 118 pounds before pregnancy to 154 pounds a week before delivery, a total increase of 36 pounds. Her blood pressure was low throughout, varying from 96/70 to 130/80 just before delivery. On most days it was 110 to 116 systolic and 70 to 80 diastolic. The urine was albumin-free throughout. There was no general edema although there was slight puffiness of the ankles before she was confined to bed. Her abdominal girth, at the level of the umbilicus, was 46½ inches, a week prior to delivery. The red blood count continued good throughout. Four days prior to delivery it read: hemoglobin, 14 Gm. (97 per cent); red blood cells, 4,560,000.

For the last four weeks of the pregnancy our residents and nurses recorded the rates of the four fetal hearts, which could be easily distinguished from each other in the four quadrants of the abdomen. It is interesting to note that the rates varied considerably and did not show any constant ratio to each other.

Fetal Heart Rates at Various Intervals in Last Month of Pregnancy

138 | 130	129 | 195	140 | 138	126 | 142
148 | 128	136 | 132	122 | 166	130 | 138

Delivery Notes.—Multiple pregnancy, multiple birth; thirty-five and one-half weeks.

A: Vertex, L. O. A.
B: Frank breech, L. S. A.
C: Vertex, L. O. A.
D: Frank breech, R. S. A.
Mediolateral episiotomy with repair.

At intervals in the last month the uterus was irritable and she leaked fluid intermittently; this increased considerably during the last week of her pregnancy. On March 19 a large piece of tissue was passed per vaginam. Examination of this showed it to be degenerated decidua.

About 3 A.M. on March 29, thirty-five and one-half weeks after the last menstrual period, contractions at five-minute intervals were noted. The patient was observed over a period of five hours, during which time the contractions became more intermittent and irregular.

Rectal examination at 8 A.M. revealed the cervix to be almost fully dilated with only a small part of the anterior lip remaining; the vertex of Baby A was at the spines.

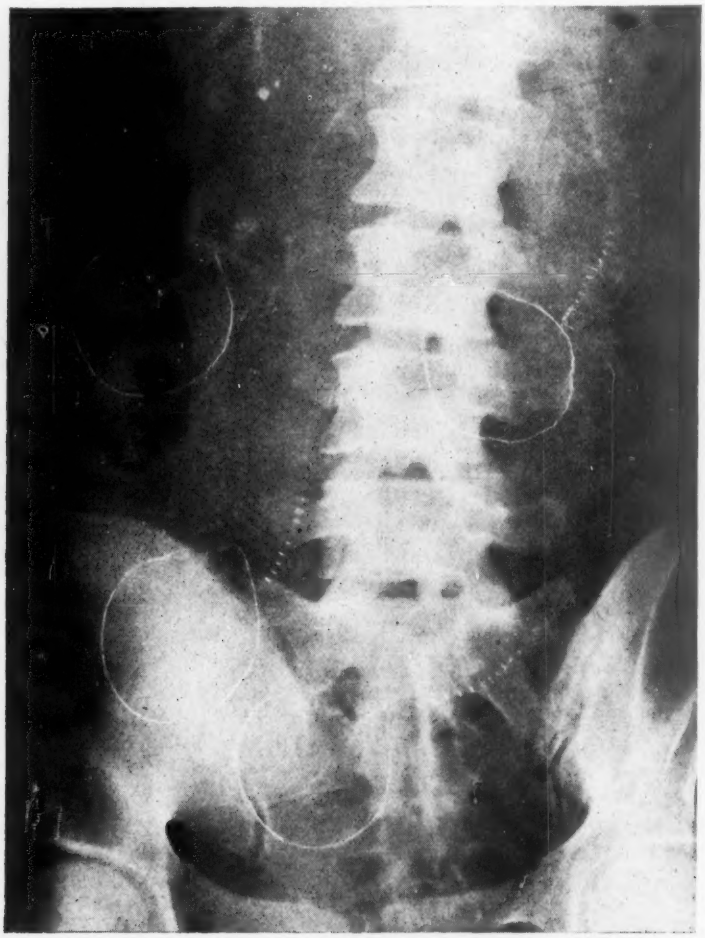

Fig. 1.—X-ray taken at four and one-half months (retouched).

She was taken to the delivery room, was given $\frac{1}{150}$ grain of scopolamine and 2 c.c. hykinone intramuscularly, and prepared for delivery. Vaginal examination confirmed the rectal examination of eight o'clock. At 10:30 A.M. the first sac was ruptured. Baby A presented by vertex, L. O. A. After short, very irregular contractions, over a period of twenty minutes, with bearing-down efforts on the part of the patient, the head descended to the pelvic floor, and following a right mediolateral episiotomy she spontaneously delivered a normal, lusty female infant. Time: 10:52 A.M.

Following delivery of Baby A, the tone of the uterus improved considerably. She was given a few whiffs of nitrous oxide and oxygen and the second sac was ruptured at 10:56 A.M.

Baby B presented as a frank breech, L. S. A. After several contractions the breech descended to the pelvic floor and delivery of a lusty male infant occurred at 11:03 A.M.

Examination then revealed Baby C presenting as a vertex. The third sac was ruptured at 11:13 A.M.

Uterine tone, momentarily, was poor and the cervix closed down to about three fingers' dilatation. Several good contractions followed, and Baby C delivered as a spontaneous L. O. A. at 11:18 A.M.

The fourth sac was ruptured at 11:21 A.M. and Baby D presented as a frank breech, R. S. A.

Uterine tone improved considerably. The breech descended to the pelvic floor and spontaneous delivery ensued of a normal, but somewhat smaller, female infant. This last baby cried rather feebly but improved rapidly. Time: 11:23 A.M.

A half cubic centimeter of pituitrin was administered following the birth of the last baby.

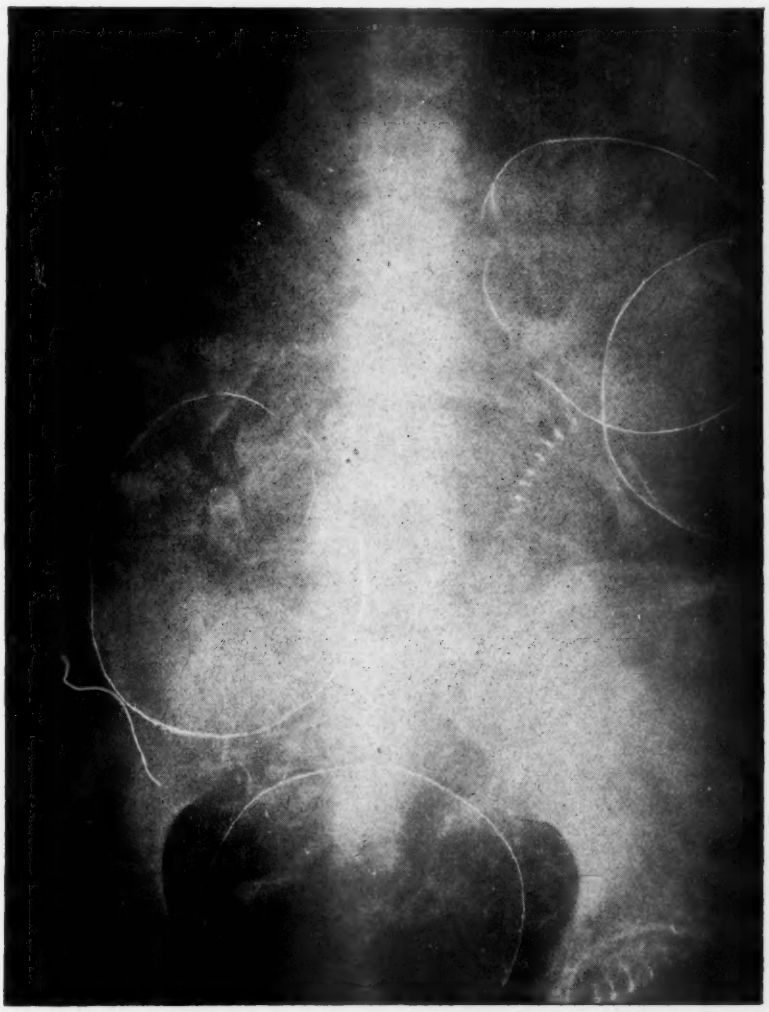

Fig. 2.—X-ray taken at seven and one-half months (retouched).

The uterus contracted down firmly; the placenta and membranes separated promptly and the third stage was concluded within seven minutes of the birth of last baby. Time: 11:30 A.M.

Estimated blood loss: 200 cubic centimeters.

Total duration of second and third stages of labor was one hour.

Another ½ c.c. of pituitrin was administered intramuscularly and 1 c.c. of ergotrate intravenously. The tone of the uterus was excellent. An infusion was started and later the normal saline was replaced with blood. Blood pressure was 120/80 at the beginning of the second stage and 130/90 at the end of the labor. A sandbag was placed on the abdomen as a precaution against dilatation of the abdominal veins. The episiotomy wound

was repaired with No. 0 chromic catgut. The anesthetic used was nitrous oxide and oxygen, which was given intermittently in small amounts as occasion demanded.

Placenta and Membranes.—The placental mass was rectangular in shape and evidently formed by the fusion of four separate units between which are definite clefts, which show on the maternal surface (Fig. 3). The color is uniformly dark brownish red. There is a notable absence of infarcts. On the fetal surface each cord is attached eccentrically within its individual amniotic sac. The cord vessels do not pass across the partitions. (Fig. 4.)

The whole placenta measured 37 cm. in length, 23 cm. in width, and 3 cm. in thickness. It weighed 1,900 grams. Size: 15 by 9 by 1¼ inches. Weight: 4⅓ pounds.

Microscopic examination of the placental tissue revealed nothing abnormal. Sections through the individual partitions between the sacs showed that each was made up of amniotic walls on each side with chorionic membrane between. The latter contained degenerated chorionic villi. (Fig. 5.)

All of these characters establish the case as one of quadriovular quadruplet pregnancy.

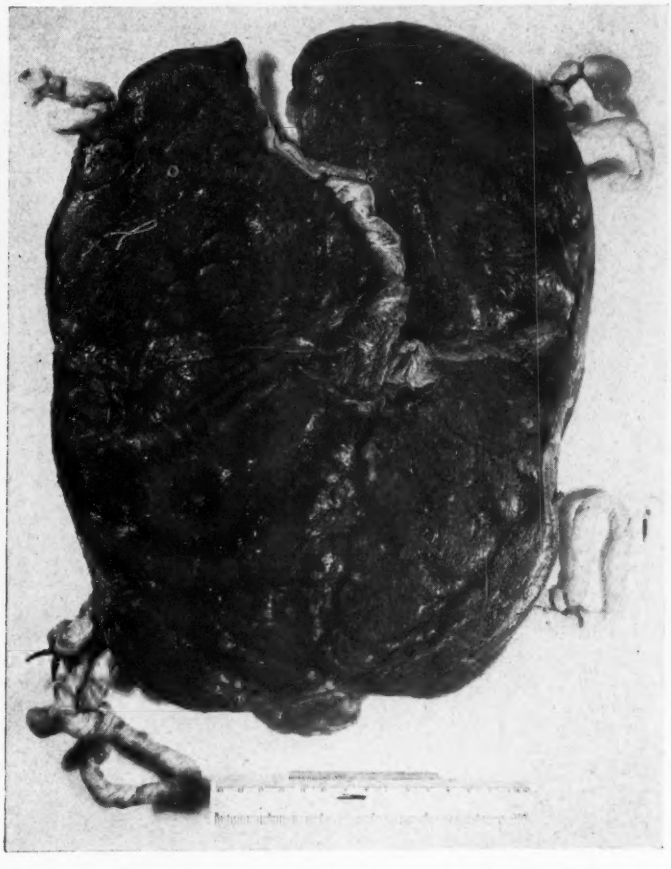

Fig. 3.—Maternal aspect of placenta. Note the definite clefts dividing it into four separate areas.

The Babies.—There were three females and one male. As already stated, examination of the placenta and membranes indicated that each was developed from a separate ovum. They are, therefore, quadriovular quadruplets. Dr. Harry J. Cohen, the pediatrician who has taken care of them since they left the hospital, reports that, at 7 months of age, they have no striking resemblances and can easily be distinguished from one another.

The preponderance of females is in conformity with the statistics of plural births. In the Statistical Bulletin of the Metropolitan Life Insurance Company of May, 1944, it is stated that "The ratio of females to males at birth appears to increase as the number of children born at one confinement increases. For single births there are 94 females born for every 100 males. For twins the figure rises to 97 per 100 males. In the higher order of plural births the sex ratio is reversed, and females are in the majority. For triplets there are 101 females born for every 100 males, and for quadruplets the ratio is as high as 156 to 100."

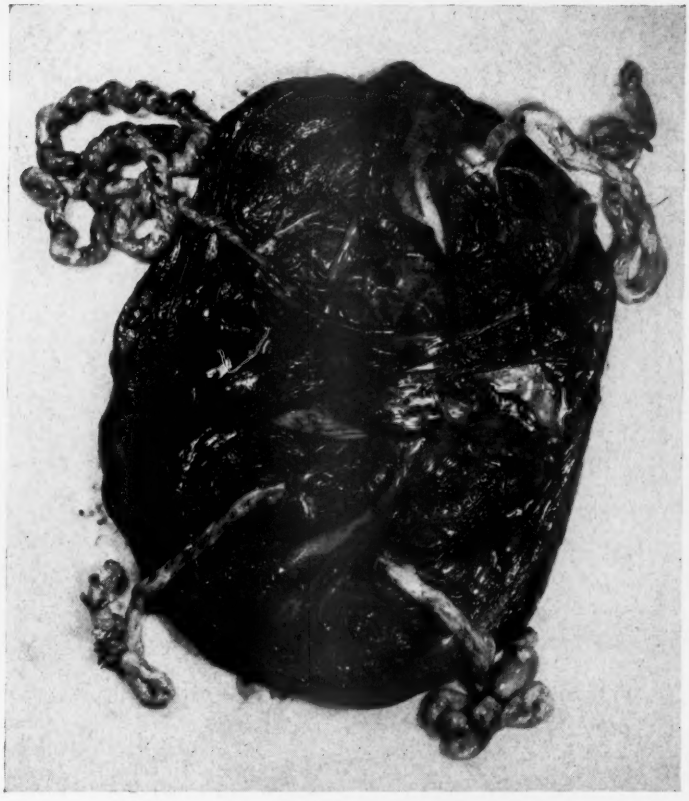

Fig. 4.—Maternal aspect of placenta. Four separate sacs with eccentric insertion of cords.

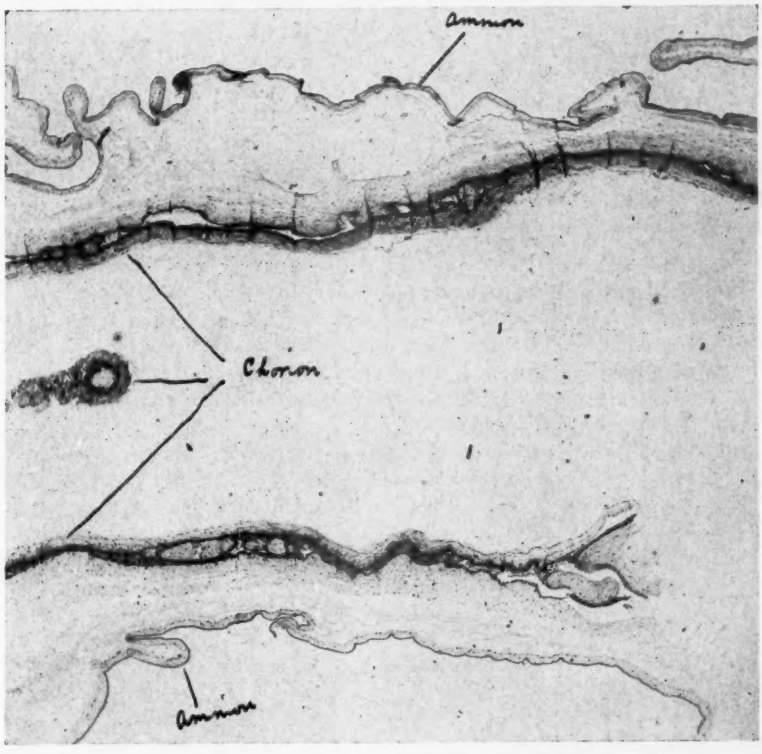

Fig. 5.—Cross section of the membranes between two of the amniotic cavities. Note the amniotic lining to each sac with the layer of chorion with degenerated villi covering it. The two chorionic surfaces are separated artificially in the preparation of the specimen.

The weights of the babies at birth were as follows:

Baby A, female, 2,270 grams (5 pounds)
Baby B, male, 2,270 grams (5 pounds)
Baby C, female, 2,160 grams (4 pounds, 12 ounces)
Baby D, female, 2,200 grams (4 pounds, 13 ounces)

After small initial losses, all of them had regained their birth weight by the eighth day, and thereafter they continued to gain so that on discharge from the hospital on the forty-eighth day they weighed, respectively: 8 pounds; 7 pounds, 11 ounces; 8 pounds, 4 ounces; and 7 pounds, 6 ounces.

At 7 months they weighed: 17 pounds, 13 ounces; 16 pounds, 1 ounce; 17 pounds, 1 ounce; and 16 pounds, 4 ounces.

All the babies were perfectly developed except Baby C who had a defect of the right ear with atresia of the external auditory canal. I am informed that a paternal aunt has a similar congenital anomaly.

All showed a fall in hemoglobin and red blood cell count following birth, and all had a moderate degree of anemia at the time of discharge from hospital. The hemoglobin percentages then were, respectively: 63 per cent, 54 per cent, 62 per cent, and 66 per cent. The red cell counts were: 2,240,000; 2,200,000; 2,400,000; and 2,540,000.

The babies were kept in incubators for a few days and then in ordinary cribs in the premature nursery. None were breast fed. All were on the usual formula for children of their weight. All were given iron in the form of ferrous sulfate.

At seven months the hemoglobin of each was 75 per cent. The children had developed normally both physically and mentally. The boy and one of the girls each had two teeth. The boy was the most active and energetic of the group. He could crawl on hands and knees the length of the crib.

Dr. Philip Levine was greatly interested in determining the blood types of the members of the family. He reported them as follows:

	Group	*Anti-Rh*	*Anti-Rh_1*	*Hr*
Father	OM	Pos.	Pos.	Neg.
Mother	OMN	Pos.	Neg.	Pos.
Baby A	OMN	Pos.	Pos.	Pos.
Baby B	OM	Pos.	Pos.	Pos.
Baby C	OM	Pos.	Pos.	Pos.
Baby D	OM	Pos.	Pos.	Pos.

The father is homozygous for the Rh factor because he is negative for Hr. Accordingly, his genotype is Rh_1Rh_1. The mother is Rh_2 and this type behaves genetically like a homozygous Hr. All offsprings must therefore be heterozygous for the Rh factors, i.e., Rh_1Rh_1 and this is exactly what is shown by the results.

Comments

The successful outcome of this case, I believe, is due to the bed rest and quiet this patient had in the last two months of her pregnancy. There was uterine irritability all through this time and toward the end there was leaking of fluid like liquor amnii and even the expulsion of a piece of degenerated decidua. Under these circumstances I believe labor would have set in much sooner had she not been kept at rest. Whether the fluid was really liquor amnii or not, I cannot be certain, but we do know that each amniotic sac was apparently intact at the time of labor. The origin of the fluid may, therefore, have been extraovular, so-called hydrorrhea gravidarum.

The ease of the labor is noteworthy. Uterine tone was fairly good throughout, increasing as each successive baby was born. All of the amniotic sacs were ruptured artificially as soon as the uterus contracted down following the delivery of the preceding child. The episiotomy minimized fetal trauma. In spite of the size of the placenta it separated and was expelled promptly and there was a minimal loss of blood.

There was no postpartum shock or fall of blood pressure following the delivery, in fact the blood pressure was higher at the end of labor than it had ever been during the pregnancy.

The puerperium was uneventful. Uterine involution was slower than average, the fundus being still palpable above the pelvic brim at the end of the second week. At the end of two months the uterus was of average size and in good position. The tone of the abdominal muscles has never been fully restored.

A PERITONEAL STAINING TECHNIQUE FOR EXTRAPERITONEAL CESAREAN SECTION

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EXTRAPERITONEAL cesarean section is steadily gaining acceptance as the procedure of choice for abdominal delivery of potentially or actually infected parturients with obstructed labor.[1-20] In spite of recent improvements in technique the operation remains difficult, and experienced operators may encounter trouble in performing it.

The commonest technical error, inadvertent puncture of the peritoneum, is corrected by ligature or suture. Subsequent dissection of the peritoneofascial flap is then complicated by a weak area liable to secondary rupture. Repair of the rent decreases the size of the flap, requiring compensatory dissection to provide room for delivery of the infant.

A peritoneal staining technique was conceived of to facilitate dissection of the peritoneofascial flap, and to aid in preventing injury to it. To accomplish this the flap is stained before its dissection by introducing dye into the peritoneal cavity. The stained peritoneum provides, in contrast to the unstained hernia-like sac sometimes difficult to locate or easily lost, a landmark to guide dissection of the peritoneofascial flap from the bladder.

Properties considered in selecting a dye for this purpose were (1) low general toxicity, (2) absence of untoward peritoneal reaction, (3) staining ability, and (4) availability. Phenolsulfonphthalein and methylene blue were chosen for experiment. The staining reaction of phenolsulfonphthalein was weak in the first clinical trial, and in subsequent operations methylene blue was found to be more satisfactory.

Peritoneal Staining Technique

After preparation of the vagina and sterile vaginal examination, the urinary bladder is emptied by catheter and refilled with about 250 c.c. of 0.001 per cent phenolsulfonphthalein solution.* The catheter is left in the bladder. A midline incision is made down to the transversalis fascia which is stripped by blunt dissection from the undersurface of the recti muscles. A small opening is then made into the peritoneal cavity at the extreme upper pole of the incision. Through this opening a soft rubber catheter, to which a syringe containing 5 c.c. of 0.5 per cent aqueous methylene blue solution has been attached, is inserted into the peritoneal cavity toward the bladder. Any free peritoneal fluid is aspirated. The bladder is then emptied and the dye injected over its peritoneal surface. Injection is performed slowly with simultaneous manipulation of the catheter tip through the transversalis fascia and peritoneum to bring the dye in contact with all of the future peritoneofascial flap. During this procedure the edges of the peritoneal opening are elevated by an assistant to prevent overflow of dye onto extraperitoneal tissues. When injection is completed the catheter is withdrawn. The peritoneum is then closed transversely with a continuous suture of fine chromic gut and the transversalis fascia longitudinally with a continuous suture of the same material. Occasionally the tissues involved will accept only one layer of suture. The resulting sharply demarcated blue peritoneum guides subsequent dissection of the peritoneal flap.

*The 0.001 per cent phenolsulfonphthalein solution is prepared by adding to 250 c.c. of sterile distilled water 24 mg. of phenolsulfonphthalein and 30 Gm. of sodium bicarbonate. Both solutions are sterilized by autoclaving.

Report of Cases

This technique has been employed in ten extraperitoneal cesarean sections. In general the indications for extraperitoneal section set forth by Cosgrove and Norton[4] have been followed. These are (1) previous vaginal examination or attempts at delivery, (2) clinical evidence of infection, (3) duration of labor in excess of twenty-four hours or (4) duration of membrane rupture in excess of eight to twelve hours. In Cases 3 and 7 the extraperitoneal route was employed electively to augment experience with the staining technique.

CASE 1.—A 26-year-old primigravida, 5 feet tall and weighing 171 pounds, was first seen on March 22, 1943. Since she was only four weeks from term, no pelvic examination was done. Overriding of the fetal head was noted two weeks later. When the patient entered the hospital in early labor, roentgenologic examination disclosed a small gynecoid pelvis with evidence of cephalopelvic disproportion. After 19 hours of strong labor and 12 hours of membrane rupture, her temperature rose to 101.6° F. The cervix was 7 cm. dilated and the head gave no promise of engagement. On April 28, 1943, an 8-pound, 6-ounce male infant was delivered by extraperitoneal cesarean section. The patient experienced one day of morbidity,* her highest temperature being 102° F. Both mother and infant left the hospital in good condition on the sixteenth postoperative day.

CASE 2.—A 21-year-old primigravida, 4 feet 10 inches tall, was first seen at thirty-five weeks' gestation. No pelvic examination was performed, but a note was made that roentgenologic examination of the pelvis should be made if the head was unengaged at the onset of labor. Such examination revealed a small gynecoid-android pelvis with much molding of the unengaged head. With unsatisfactory progress during 27 hours of labor and 9 hours of membrane rupture, extraperitoneal cesarean section was performed on May 5, 1943, with delivery of a 7-pound, 2-ounce male infant. The patient experienced one morbid day, and was discharged from the hospital in good condition on the fifteenth postoperative day.

CASE 3.—A 35-year-old secundigravida, whose first pregnancy three years previously had terminated in spontaneous birth and neonatal death because of cerebral hemorrhage of a 6-pound 9-ounce infant, entered the hospital in early labor. Clinically her diagonal conjugate had measured 9.5 cm., and x-ray had disclosed a platypelloid pelvis. After 10 hours of moderate labor without promise of engagement of the overriding head, pregnancy was terminated on May 22, 1943, by cesarean section, by election of the extraperitoneal type. The infant weighed 6 pounds, 10 ounces. The patient experienced no morbidity; both she and her infant left the hospital in good condition on the twelfth postoperative day.

CASE 4.—A 35-year-old primigravida was noted during her prenatal course to have a small gynecoid pelvis. Going into labor at thirty-nine weeks' gestation with a frank breech presentation, she made satisfactory progress until the cervix was completely dilated, after which the breech failed to advance during a nine-hour period. After 16 hours of labor with an equal period of membrane rupture, extraperitoneal cesarean section was performed on July 14, 1943, with delivery of a 6-pound 2-ounce female infant. The patient experienced two morbid days, her highest temperature being 101° F. Both she and her infant were discharged from the hospital in good condition on the eighteenth postoperative day.

CASE 5.—A 25-year-old primigravida, 4 feet 10 inches tall, with a small gynecoid pelvis by both clinical and x-ray examination, failed to engage the head after 27 hours of labor and eight hours of membrane rupture. An 8-pound 12-ounce male infant was delivered by extraperitoneal cesarean section on Aug. 14, 1943. The patient experienced two morbid days, her highest temperature being 101.2° F. She and her infant were discharged in good condition on the thirteenth postoperative day.

CASE 6.—A 33-year-old primigravida with an apparently adequate gynecoid pelvis by both clinical and roentgenologic examination went into labor at term. A better than average-sized fetus presented in right occipitoposterior. After 46 hours of labor and 28 hours of membrane rupture, the cervix, although well effaced, was only 3 cm. dilated, and the liquor amnii had become foul. The lower uterine segment was tender, and so thin that the infant's

*Morbidity Standard: Temperature 100.4°F. or above on any day excluding the first twenty-four hours after delivery.

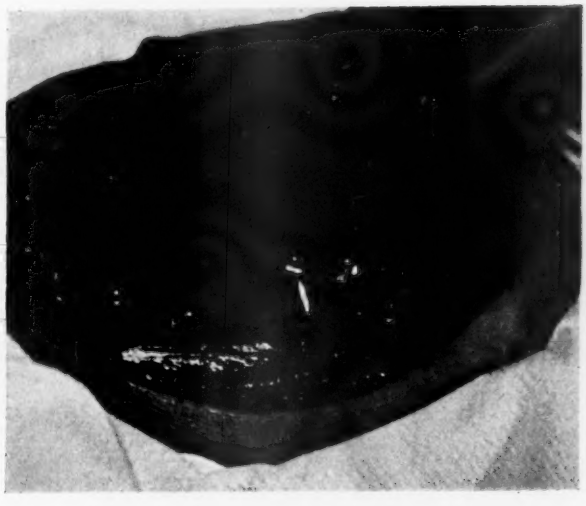

Plate I.—The stained peritoneofascial flap is elevated from the lower uterine segment. The bladder appears at the inferior angle of the incision. (Engraving from Official Photograph, U. S. Army Air Corps, Base Photo Section, Mitchel Field, N. Y.)

chin and anterior arm could be easily palpated through the abdominal wall. A 9-pound 6-ounce male infant was delivered by extraperitoneal cesarean section on Oct. 3, 1943. During its dissection the peritoneofascial flap was inadvertently torn by traction. A velvety smooth blue peritoneal surface presented through the rent. There was no detectable free fluid and no escape of methylene blue onto the extraperitoneal tissues. The tear was immediately repaired. The patient experienced four morbid days, her highest temperature being 102.4° F., and she was discharged with her infant in good condition on the seventeenth postoperative day.

CASE 7.—A 26-year-old primigravida, 4 feet 10 inches tall, presented a small platypelloid pelvis with diagonal conjugate of 9 cm. on antepartum pelvic examination. After 17 hours of moderate labor during which the head persistently overrode the symphysis, an 8-pound 6-ounce male infant was delivered on Oct. 30, 1943, by the abdominal route, by election of extraperitoneal type. The patient experienced two morbid days, her highest temperature being 102.4° F. She was discharged from the hospital with her baby on the thirteenth postoperative day.

CASE 8.—A 21-year-old primigravida with a gynecoid-android pelvis went into labor at forty-five weeks' gestation by date. After 80 hours of labor, of which 56 hours were considered effectual, and after 33 hours of membrane rupture, the liquor amnii was becoming foul. The cervix was 4 cm. dilated. A 7-pound 11- ounce male infant was delivered on Nov. 29, 1943, by extraperitoneal cesarean section using 2.5 c.c. of methylene blue solution. The peritoneofascial flap was incompletely stained, and accidentally punctured in an unstained area. The puncture was immediately repaired. The patient experienced two morbid days, her highest temperature being 103.8° F., and was discharged in good condition, together with her infant, on the thirteenth postoperative day.

CASE 9.—A 23-year-old primigravida at term presented an unengaged head after 38 hours of labor and an equal duration of membrane rupture. The cervix had remained 6 cm. dilated for eight hours. A 7-pound 4-ounce female infant was delivered by extraperitoneal cesarean section on April 21, 1944. Because the methylene blue solution was injected in the presence of a distended bladder, the peritoneofascial flap was incompletely stained. The flap was accidentally punctured, and immediately repaired. The patient experienced four morbid days, her highest temperature being 103.2° F., and was discharged together with her infant on the nineteenth postoperative day.

CASE 10.—A 28-year-old primigravida at thirty-nine weeks' gestation entered the hospital in early labor with a frank breech presentation. The membranes had ruptured two hours after the onset of labor. The cervix was completely dilated and the breech in midpelvis after nine hours of labor. Because no further descent of the breech occurred during the next five hours, sterile vaginal examination was performed. It revealed firm soft tissues and a gynecoid pelvis which seemed adequate except for a contracted outlet. Roentgenologic examination confirmed the latter. During eight hours subsequent labor, the uterine contractions became weaker and less frequent, and no further advance of the presenting part occurred. It was explained to the patient, whose husband was overseas, and to her mother that choice of management lay between breech extraction and cesarean section. The maternal and fetal hazards of each were stated. They chose abdominal delivery. After 22 hours of labor and 20 hours of membrane rupture, an extraperitoneal cesarean section was performed on July 17, 1944. The infant, whose weight had been judged average prior to delivery, weighed 4 pounds, 14 ounces. The patient experienced two morbid postoperative days, her highest temperature being 101.4° F. She left the hospital together with her infant in good condition on the fifteenth postoperative day.

Case 4 was the first extraperitoneal cesarean performed by one member of the surgical staff; it was accomplished with facility. Cases 1, 2, 3, 5, 7, 8, 9, and 10 were performed by the writer. There were no bladder or ureteral injuries. Postoperative abdominal distention was minimal, nausea was rare, and there was no postoperative vomiting in any case. In no instance did evidence of peritoneal irritation develop. The urine of all patients was free of methylene blue within forty-eight and usually within thirty-six hours of operation. Postoperative morbidity averaged two days. The postoperative hospital stay averaged fifteen days. There was neither maternal nor fetal mortality. Six-week and subsequent postpartum examinations have shown that all ten patients possess well-involuted and freely movable uteri.

Technical Considerations

The dark blue edge of the stained peritoneofascial flap serves as a reliable guide for dissecting it from the bladder and uterus. There is clear delineation of the inferior margin of the parietovesical peritoneal fold. The latter varies from patient to patient in contour, symmetry or lack of it, and level of bladder attachment. The initial incision through the transversalis and anterior perivesical fasciae is made transversely about ½ inch below the stained fold. The perivesical fascia is then bluntly dissected from the bladder muscularis laterally to the point of junction of the bladder, uterus, and stained uterovesical fold of peritoneum. The latter constitutes a landmark for accurate incision through the posterior perivesical and anterior periuterine fascial layers, exposing the anterolateral aspect of the lower uterine segment. Dissection to the same degree is repeated on the opposite side of the bladder. The two anterolateral areas of lower uterine segment thus exposed are then made continuous by blunt dissection with the finger of the entire uterovesical fold from the lower uterine segment. This frees the bladder circumferentially so that it is attached to the peritoneofascial flap only on its superior surface. Gentle traction on these structures then permits their complete separation by sharp and blunt dissection. As others have noted, division of the peritoneofascial flap from the bladder in the urachal area usually requires sharp dissection.

Strands of tissue stained by methylene blue may be found in the more adherent urachal area, and occasionally in the superolateral areas of the exposed lower uterine segment. Such areas present a variegated appearance, however, and are presumably the result of absorption of methylene blue into lymphatic channels draining the peritoneum. There is still good contrast between the bladder or uterus and the stained peritoneofascial flap, and in no instance has anatomical confusion arisen because of these areas.

In three cases the peritoneal cavity was inadvertently entered. In Case 6 the posterior fold of the peritoneofascial flap was accidentally torn by undue traction twenty minutes after injection of the dye. The solution had been completely absorbed. In Case 8 where an attempt was made to reduce the quantity of methylene blue solution to 2.5 c.c., there was incomplete staining of the peritoneofascial flap and it was accidentally opened in the unstained area. In Case 9 the methylene blue solution was injected into the peritoneal cavity in the presence of a distended bladder. This resulted first in slight overflow of the solution at the site of injection, and second in incomplete staining of the peritoneofascial flap with its subsequent violation. These experiences emphasize the importance of injecting an adequate amount of dye solution in the presence of an empty bladder.

Discussion

Criticism may be directed at intentional opening of the peritoneal cavity in an operation whose primary purpose is elimination of peritonitis. However, the peritoneal incision is placed where both tension on the peritoneofascial flap and likelihood of tearing it during subsequent dissection are minimal. As an added precaution the incision is closed, when possible, in two staggered layers. Regardless of the manner of closure, no leakage of dye through the peritoneal incision has occured in any of the operations performed; it follows that bacteria are unlikely to penetrate in the reverse direction.

There is a possibility that accidental rupture of the peritoneofascial flap will permit the escape of dye onto the extraperitoneal tissues thus creating anatomical confusion. In the one instance where the stained flap was torn by undue traction twenty minutes after injection of the dye, no dye escaped. It had been absorbed within that time. Only further experience can answer the questions of how long such absorption requires, and what the result of rupture before absorption of the dye may be.

Contrary to what one might expect, handling of the stained peritoneofascial flap does not result in staining of gloves, instruments, or the operative field.

Objection may be made to calling a section performed by the peritoneal staining technique extraperitoneal. Since most reported series of extraperitoneal cesarean sections include operations where the peritoneal cavity has been

violated, and since the purpose of extraperitoneal operation in regard to the patient's welfare is accomplished in spite of such violations, there is some argument for classifying the peritoneal staining technique with other extraperitoneal operations. It is suggested that techniques where the peritoneum is deliberately opened and then closed, such as that of Aldridge[1] and the one described here, might be termed pseudoextraperitoneal. This would distinguish such operations from both the true extraperitoneal operations and those performed by peritoneal exclusion.

Summary

A peritoneal staining technique to facilitate recognition of the peritoneofascial flap and aid in preventing its accidental puncture is presented. A single small premeditated opening is made into the peritoneal cavity to permit injection of dye substance in the area of the future peritoneofascial flap. Five cubic centimeters of 0.5 per cent aqueous methylene blue solution, introduced through the peritoneal opening by catheter, has been found satisfactory for this purpose. It is important that the bladder be empty during injection of the dye. The peritoneal incision is closed before dissection of the flap is begun. Demarcation of the peritoneum by color provides a reliable guide for dissection of the peritoneofascial flap.

Ten extraperitoneal cesarean sections have been performed in this manner without maternal or fetal mortality. The peritoneal cavity was accidentally entered three times, once because of undue traction on the peritoneofascial flap, twice because the flap was incompletely stained. Incomplete staining of the peritoneofascial flap occurred in the first instance because the amount of dye was insufficient; in the second because injection of the dye was performed in the presence of a distended bladder. There was no injury to bladder or ureters. Convalescence of all patients was free of any peritoneal irritation or postoperative vomiting. All uteri were well involuted and freely movable at follow-up examinations.

Various considerations arising from use of the technique are discussed.

References

1. Aldridge, A. H.: Am. J. Obst. & Gynec. **33**: 388, 1937.
2. Briscoe, C. C.: Am. J. Obst. & Gynec. **48**: 16, 1944.
3. Burns, H. T.: Am. J. Obst. & Gynec. **19**: 759, 1930.
4. Cosgrove, S. A., and Norton, J. F.: J. A. M. A. **118**: 201, 1942.
5. Cooke, W. R.: Am. J. Obst. & Gynec. **35**: 469, 1938.
6. Daichman, I., and Pomerance, W.: Am. J. Obst. & Gynec. **47**: 678, 1944.
7. Eisaman, J. R., and Austin, B. R.: Pennsylvania M. J. **45**: 813, 1942.
8. Irwin, L. C.: West. J. Surg. **49**: 158, 1941.
9. King, E. L.: Am. J. Obst. & Gynec. **40**: 860, 1940.
10. Manahan, C. P., Connally, H. F., Jr., and Eastmen, N. J.: Am. J. Obst. & Gynec. **44**: 999, 1943.
11. Marr, J. P.: New York State J. Med. **44**: 1230, 1944.
12. Norton, J. F.: Am. J. Obst. & Gynec. **40**: 209, 1940.
13. Phaneuf, L. E.: Am. J. Obst. & Gynec. **40**: 603, 1940.
14. Idem: Discussion of article by Mohler, R. W.: Am. J. Obst. & Gynec. **45**: 466, 1943.
15. Pieri, R. J., and Irving, F. R.: New York State J. Med. **42**: 25, 1942.
16. Ricci, J. V.: Am. J. Surg. **47**: 33, 1940.
17. Steele, K. B.: Am. J. Obst. & Gynec. **19**: 747, 1930.
18. Waters, E. G.: Am. J. Obst. & Gynec. **39**: 423, 1940.
19. Idem: West. J. Surg. **50**: 512, 1942.
20. Williamson, H. C., and Goldblatt, M. E.: Am. J. Obst. & Gynec. **45**: 103, 1943.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

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THE Fallopian tubes, by repute, are highly resistant to malignant disease. Primary tubal carcinoma is one of the most rare of gynecologic tumors. Less than four hundred cases have been reported in the literature to date. From a consecutive series of 30,000 gynecologic admissions to the Women's Pavilion of the Royal Victoria Hospital, only two cases were found. In 1925 it was remarked by S. J. Cameron[1] that this disease was so rare that many gynecologists had never encountered it. It fell to the lot of one of us (W. A. G. B.), to find both our cases at operation.

It occurs chiefly in the cancer age (40 to 60 years) although cases have been reported as early as the second decade and as late as the eighth. It is bilateral in about one-third of the cases. Multiple pelvic pathology has been found in association in most cases, e.g., chronic salpingitis, ovarian cystomata, uterine fibroids, etc.

Some authors have expressed the view that salpingitis was a precursor of the disease, predisposing to its onset. In opposition to this opinion, it may be reasoned that salpingitis is the commonest tubal disease while malignancy is the most rare. Therefore, there must be other more potent etiological factors concerned in its production. The associated inflammatory features in this case are most interesting as will be shown later.

According to Doran[2] the presence of the tumor itself may produce a chronic inflammatory reaction, which may close the tube and simulate a hydrosalpinx. This proves to be a defense mechanism slowing the spread via the tubal ostium. In addition, pressure within the closed sac produces pain which should cause the patient to seek medical advice at an earlier date. When the tube is open there may be no symptoms until the abdomen begins to enlarge because of ascites and peritoneal metastases.

In an effort to explain the relative infrequency of tubal as compared with endometrial cancer it is interesting to contrast the two epithelia. Both tissues arise from the Müllerian ducts. The uterine epithelium is extremely active and is constantly in a state of flux, blossoming forth so resplendent in response to the ovarian growth and secretory hormones, only to wilt and die quickly on the sudden withdrawal of its nourishing stimulus, at the termination of its short fruitless cycle It undergoes tremendous hypertrophy during pregnancy and is exposed to much more injury and rapid transformation than is the tubal mucosa. In contrast, the tubal epithelium is quite inactive and is well protected. Although it reacts to the cyclic changes of menstruation, they are insignificant. There is no monthly desquamation to be followed by rapid regeneration, and even during pregnancy the tubal mucosa alters little. Therefore, it would seem that these conditions produce a situation which offers scant opportunity for cellular overgrowth, hyperplasia, or unusual cytologic activity.

When found in its early stages, the tumor may be represented merely by a firm nodular thickening resembling an olive or a sausage enclosed within an intact tubal wall. In some cases a hydrosalpinx or a hematosalpinx may be found proximal to the tumor. This association would tend to confuse the diagnosis grossly, suggesting a purely inflammatory condition.

In the advanced case the gross appearance is that of a large ovoid mass simulating a pyosalpinx except that the external surface is smooth and solid and free of adhesions. The tubal orifice may be open, in which case papillary projections frequently grow out, spreading along the peritoneum, pelvic and abdominal organs by direct extension.

When the tube is sectioned transversely, the center is filled with a thickened papillary mass which is friable, hemorrhagic, and necrotic in some areas, growing on a fibrous groundwork with connective tissue septa running throughout. The tubal wall may be of normal thickness or it may be very thin over the mass due to stretching.

Two microscopic types were originally described by Sänger and Barth, the papillary and the papillary alveolar. Most cases have been placed in the first group, the papillary tendency being the predominant characteristic, while those cases exhibiting a glandular pattern have been relegated to the latter group. Some of the more recent authors are in agreement with Liang[4] who, in 1926, following a careful pathologic study of the subject, arrived at the conclusion that there was only one type, the alveolar morphologic arrangement representing merely a different stage of the process.

Wharton and Krock[6] state that their series of 14 cases showed an identical histological pattern, with only minor variations in growth and morphology. They state that although it may be true that some tumors are largely alveolar and others papillary, there is at present no evidence that they are inherently distinct or that their behaviour is different in regard to malignancy, methods of extension, or clinical characteristics.

The neoplasm has its origin in the tubal mucous membrane. There is a tendency at first glance to label the lesion as an adenocarcinoma of the tube. But this in incorrect as there are no glands in the tube. Abnormal growth merely produces a pseudoglandular picture. Various stages of metaplasia may be observed in any one case. In some areas small papillary growths replace the fine wavy tufts of normal mucosa. In these papillae there is little connective tissue framework, the growth consisting chiefly of single layers of tubal epithelium, arranged in glandlike pattern, suggesting the picture found in adenocarcinoma of the endometrium. The epithelial cells themselves may show no abnormal change but the pattern shows malignant disease. Our case, however, shows malignant cytology as well as morphology.

In other papillae in which the process is further advanced, there is a heaping up of epithelium so that it may be several layers thick or may even form solid nests of cells. The cells become more and more irregular in shape and atypical and the nuclei become hyperchromatic.

Large overgrown plicae appear to grow centrally from a notably intact wall. The tubal wall is usually free from invasion. As the papillae enlarge and press against each other, they unite to form solid masses of tissue. The alveoli are filled with hyaline secretion and the papillae tend to lose their individuality.

Mitotic figures, lymphocytic infiltration, and occasional areas of necrosis appear. This stage corresponds to the so-called papillary-alveolar type.

It should be noted in passing that extensive tubal tuberculosis may produce an adenomatous structure strikingly similar to that of malignancy, and careful study is necessary to permit an accurate differentiation.

Case Report

The patient was 51 years of age, born in Canada of Aryan stock, admitted to the Women's Pavilion of the Royal Victoria Hospital on Oct. 10, 1942. She complained of pain of an intermittent character in the left lower quadrant, first noticed twelve months ago. The pain radiated through to the back and occasionally down the left leg. For the past six months the severity of attacks had been exaggerated and one month ago bleeding from hemorrhoids had been noticed for the first time. Menstrual history unaltered. Cycle: 12 by 28 by 3. No menometrorrhagia, leucorrhea, or dysmenorrhea. Attacks of pain more frequent postmenstrually. Patient had been married nineteen years and had never been pregnant. Of interest in her past history was the fact that twelve years ago she underwent an operation to overcome sterility. The patient had been married seven years at this time without becoming pregnant. Postoperatively she developed pelvic cellulitis and phlebitis necessitating hospitalization for three months. Subsequently, a complete recovery was made and she had enjoyed good health up to the onset of the present trouble.

The family history was negative for cancer.

On examination a firm mass was felt in the pelvis on the left side and a laparotomy was performed.

At operation a mass the size of a baseball was found in the left tube extending into the broad ligament, its surface appearing smooth, convoluted, and congested. The fimbriated end of the tube was closed. On the opposite side a smaller tumor the size of an egg was found in the right tube. Both ovaries exhibited a normal appearance showing no involvement with the tumor growth. A panhysterectomy was performed.

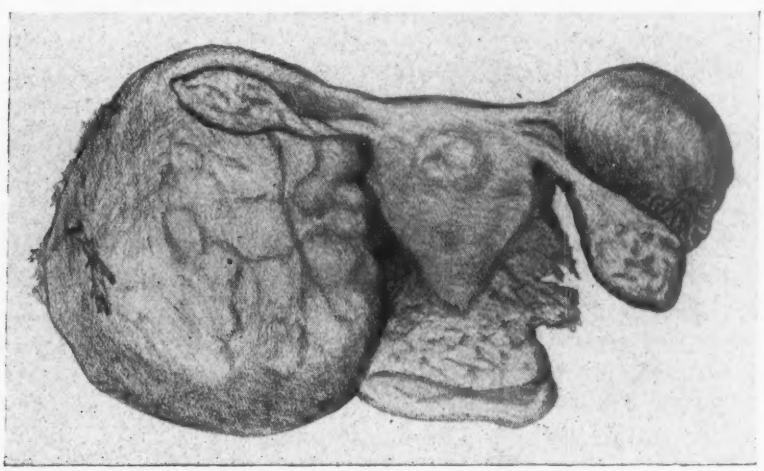

Fig. 1.—Gross appearance of pelvic organs following removal. Note the large tumor mass on the left side completely enclosed in enormously stretched tubal wall. The smaller tumor on the right presented a more smooth and firm consistency.

Gross examination of the removed organs revealed a normal-sized uterus measuring 8 by 6 by 4 cm. removed with cervix attached (Fig. 1). One or two marble-sized fibroids appeared on the posterior surface of the uterus. The endometrium appeared smooth and showed no gross lesion. The left adnexa exhibited a soft spherical tumor measuring 12 cm. in diameter, the surface of which consisted of the stretched tubal wall. The fimbriated end of the tube was closely bound to the tumor mass and the tubal ostium was closed. The left ovary appeared small and discrete. The right tube contained a small tumor located in the middle third of the tube, the mass appearing ovoid in shape measuring 6 by 4 cm. The right ovary was of normal size and was entirely free of adhesions and induration. When the tubal wall covering the larger tumor mass was incised, the tissue appeared soft and edematous, somewhat resembling decidual tissue. The tissue cut with a puttylike consistency and the outer part appeared quite homogeneous and numerous small spaces were opened up,

suggesting a glandular character. Towards the center of the mass, the fibrous stroma presented an arborescent appearance some parts of which were quite dense and exhibited a yellowish coloration resembling that of a corpus luteum. The smaller tumor exhibited similar characteristics except that its consistency was more firm and rubbery and its structure was homogeneous throughout.

Microscopic study of the tubal masses showed a mixed picture, the predominant characteristic being a formation of many huge hypertrophic plicae covered by extremely hyperplastic immature-appearing tubal epithelium with numerous papillary projections and dense adenomatous formations. (Fig. 3.) The epithelial tissue consisted of tall columnar

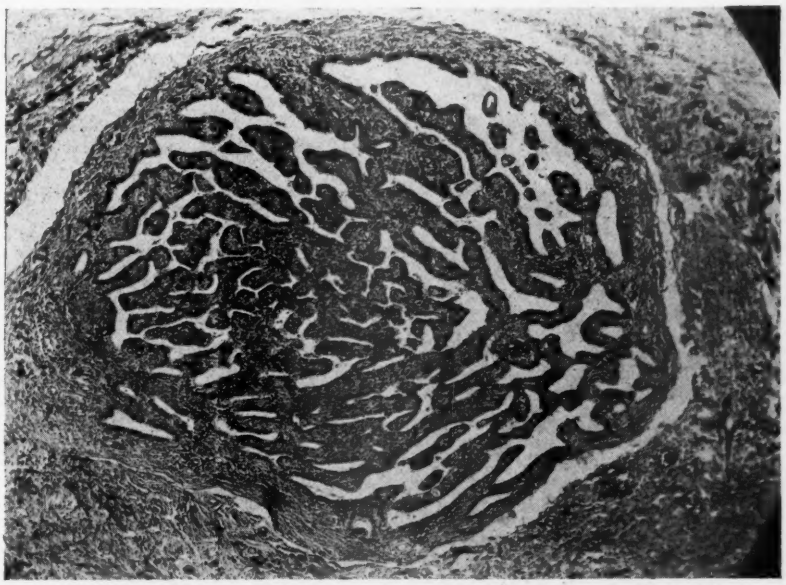

Fig. 2.—Honeycomb appearance with extensive agglutination of plicae simulating chronic follicular salpingitis.

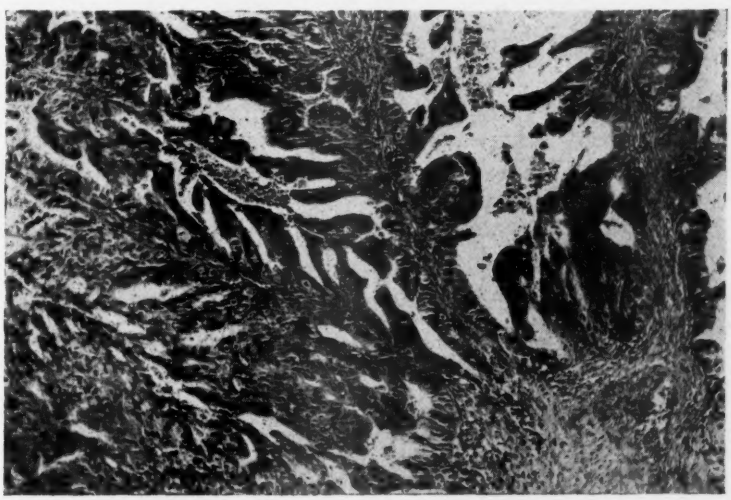

Fig. 3.—High-power study of plicae reveals malignant character of covering epithelium.

cells which in many areas appeared closely packed, tending to produce a solid structure in which there is noted pleomorphism and polychromasia, many of the nuclei appearing large and clear-staining with pyknotic nucleoli and numerous mitoses. Sections of the smaller tumor exhibited a uniformly solid sarcomatoid appearance (Fig. 4), with a pseudoglandular structure. Serial sections of the left tube taken from the cornual end distally toward the tumor show an interesting picture. In the cornual region the lumen is small with a few

stellate plicae covered by an epithelium exhibiting a hyperplastic tendency with some vacuolation. Another section of the tube more distally shows an extensive agglutination of the plicae producing a uniform honeycomb appearance throughout the lumen. The epithelium in this section appears quite benign, and the general appearance simulates an extensive follicular salpingitis (Fig. 2). Closer to the tumor the structure exhibits a more solid follicular appearance, while at the same time, the epithelium becomes more hyperplastic, assuming a more malignant structure (Fig. 3). Sections through the tumor proper present a variable appearance. Some show hyperplastic, but benign epithelium, while the morphologic structure is that of malignancy. Other sections present a definite picture of malignancy (Fig. 3) with invasion of the wall in some areas, although no area showed a complete breakthrough onto the surface.

The smaller tumor exhibited a different picture, in some areas the papillae appearing close-packed, producing a solid, almost sarcomatous appearance.

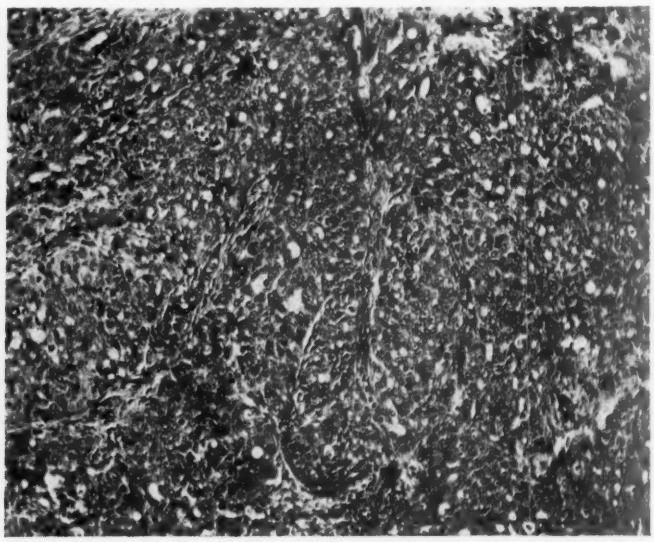

Fig. 4.—Solid arrangement found in smaller tumor presenting sarcomatoid appearance.

Discussion

Tubal carcinoma is a highly malignant lesion and very few cases are on record of a five-year cure. Spread occurs by lymphatic extension to the uterus and ovaries because of their proximity. In the first case reported from this Clinic in 1932, Kearns[3] claimed that "metastasis occurred by invasion of the subepithelial structures of the mesosalpinx spreading by way of the lymphatics to the lumbar glands." Direct spread through the ostium of the Fallopian tube, implanting on pelvic and abdominal organs, seems to be quite frequent. This spread by "spill" often occurs early in the disease, leading to rapid dissemination and death.

Rarely are implants observed in the endometrium although fluid is believed to pass down from the tube and out via the vagina.

A striking difference between primary and secondary tubal cancer is the fact that primary almost never invades the tubal wall, whereas secondary growths almost always invade the tube from without.

The disease is seldom diagnosed clinically and infrequently is it made on the operating table. Usually the true nature of the lesion is only revealed by microscopic examination. This is unfortunate. The delayed diagnosis has added greatly to the mortality rate. Wharton and Krock estimate that fully two-thirds of the reported cases have had incomplete operations, a unilateral

salpingectomy being performed for supposed hydrosalpinx. Possibly the mortality figures would appear more favorable if the mass were sectioned at the time of the operation, the tentative diagnosis made, and a panhysterectomy performed.

Pain is the most characteristic symptom, produced by the stretching of the tubal wall. An abnormal vaginal discharge is almost always associated. This is usually profuse and of a purulent, watery or sanguineous character. Some authors have reported a symptom complex, in which severe lancinating pains are suddenly relieved by the release of a profuse watery discharge per vaginam. They express the opinion that the tubal tension of the accumulating fluid is relieved by the fluid forcing its way through the cornua and discharging from the uterus and vagina.

Menstrual disorders, backache, bladder symptoms, fever, gastrointestinal disorders, abdominal ascites, and cachexia may develop as the disease spreads. The pain is frequently sharp and colicky and may be accompanied by nausea and emesis. It tends to occur from month to month, increasing in severity as the disease progresses.

The mortality from primary carcinoma of the tube is extremely high. In 1926, Wechsler[5] found only six three-year cures in 200 cases. The prognosis in this form of cancer should be better because pain is the first and most characteristic symptom, and this is what usually sends the patient to the doctor. Further, the tubal wall is seldom invaded, and, in those cases where the tubal ostium remains closed off, direct spread should not be rapid. In this case, symptoms of pain were noted for almost a year prior to operation at which time there was no gross evidence of spread. The extremely pessimistic statistics certainly paint a hopeless picture. Possibly, lymphatic metastasis occurs quite early. It must be borne in mind, however, that the figures presented are misleading. As we have stated above, fully two-thirds of these had incomplete operations. In addition, operation would tend to be delayed if the accompanying inflammation was diagnosed. Radiotherapy has been tried but with poor results, presumably for the same reasons that this form of therapy has proved disappointing in ovarian carcinoma.

This case of primary bilateral carcinoma of the tube presents several points of interest. The tissues appear generally quite clearcut and free from extensive necrotic degeneration which might otherwise destroy the cytology. While certain sections present a papillary appearance, others present a pseudoglandular or alveolar appearance. The second smaller tumor presents a definitely solid structure and so might be termed a solid carcinoma of the tube. This demonstrates that these are not three independent types of tubal carcinoma: the papillary, the alveolar, and the solid; but merely local variations in morphology.

The gradation of hyperplasia as shown in the serial sections, from the normal through the inflammatory stage to the malignant, is interesting. In view of the past history of tubal inflammation and sterility, one wonders how much of the follicular salpingitis (Fig. 2) may be a result of this, and how much may be the result of the presence of the malignancy. The theory that inflammation predisposes to malignancy would seem to be largely discounted as a major factor in as much as salpingitis is so common, and tubal carcinoma so rare. It would seem more logical that some inflammatory reaction would develop due to the presence of a tumor mass in the tube.

With such a formidable array of mortality statistics the prognosis would naturally be guarded in any case of carcinoma of the tube.

References

1. Cameron, S. J.: Brit. M. J. 2: 285, 1925.
2. Doran, Alban: J. Obst. & Gynaec. Brit. Emp. 6: 285, 1904.
3. Kearns, P. J.: Canad. M. A. J. 26: 73, 1932.
4. Liang, Z.: Virchows Arch. f. Path. Anat. 259: 577, 1926.
5. Wechsler, H. F.: Arch. Path. 2: 16, 1926.
6. Wharton, L. A., and Krock, F. H.: Arch. Surg. 19: 849, 1929.
7. Mullins, D. F., and Mosteller, R.: Am. J. Obst. & Gynec. 45: 1042, 1943.

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RELATIONSHIP OF MATERNAL WEIGHT GAIN AND WEIGHT OF NEWBORN INFANT*

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MODERN obstetric practice with its emphasis on regular antepartum care and examination has materially contributed to the elimination of many possible complications of pregnancy and labor. There still remains, despite all this, the danger of encountering the large baby in labor. This problem has gained the attention of many, and numerous contributions have been made concerning the weight changes during pregnancy and the relation of mothers' gains to the weight of the newborn infants. Studies in the past have attempted to give some basis of anticipating the probable size of the fetus. Davis,[1] Slemons and Fagan,[2] Bingham,[3] and Hanley[4] have indicated that the weight of babies at term parallel the gains of mothers. McIlroy and Rodway[5] reported that the weight of the infant was not directly dependent upon the increase in weight of the mother. Cummings[6] believes that heredity plays the most important part in determining the size of the newborn infant, although the state of health of the mother would influence it to some extent. Toombs[7] concluded that "the size of the child at the time of delivery is determined by factors quite distinct from this consideration, and in most instances, entirely beyond our control."

In view of these discrepant opinions we deemed it advisable to reinvestigate this problem and to subject our findings to statistical analysis.

This paper deals with the data of 979 parturient cases in which the mothers' gains and the weights of the newborn infants were recorded and examined to determine the existence, if any, of relationship between them. The cases were collected from the records of private patients who were delivered by members of the obstetric staff at the Beth-El Hospital between Jan. 1, 1942, and Dec. 31, 1943. The case records were examined and the selection of cases was based upon the following criteria:

They were cases of single pregnancies in which the patient began antepartum care before twelve weeks of gestation and was followed regularly to term.

*Presented at a meeting of the Brooklyn Gynecological Society, Oct. 6, 1944.

Onset of labor was spontaneous within fourteen days of the expected date of the confinement; delivery was by the pelvic route with the birth of a normal living infant.

The parturients were normal patients without pre-existing disease and without any disease noted during the antenatal period. A number of them had mild symptoms such as nausea with occasional vomiting, which were corrected. Excess weight gains were noted, in some instances, with evidences of edema. These were not accompanied, however, by any abnormality such as albuminuria or elevation of blood pressure.

Well-balanced diet and fluid balance were stressed and occasionally vitamin supplements were administered. No attempt was made, however, to administer treatment with special diets. The data will be shown in Table I and Fig. 1.

TABLE I. MOTHER'S GAINS AND WEIGHTS OF BABIES (TOTAL GROUP A—979 CASES)

MOTHER'S GAINS IN POUNDS*	AVERAGE WEIGHT OF BABY		BABIES	MALES	FEMALES	AVERAGE WEIGHT OF MALE		AVERAGE WEIGHT OF FEMALE	
	(LB.)	(OZ.)	(NO.)	(NO.)	(NO.)	(LB.)	(OZ.)	(LB.)	(OZ.)
0 to 5	6	8	8	4	4	6	12	6	4
5 to 10	7	5	26	11	15	7	12	7	
10 to 15	6	13	83	46	37	6	15	6	11
15 to 20	7	1	237	115	122	7	2	7	1
20 to 25	7	3	312	168	144	7	5	7	
25 to 30	7	5	201	103	98	7	5	7	
30 to 35	7	6	78	42	36	7	7	7	6
35 to 40	7	12	24	13	11	7	14	7	9
Over 40	8	2	10	5	5	8	2	8	2

*0 pounds up to but not including 5 pounds, etc.

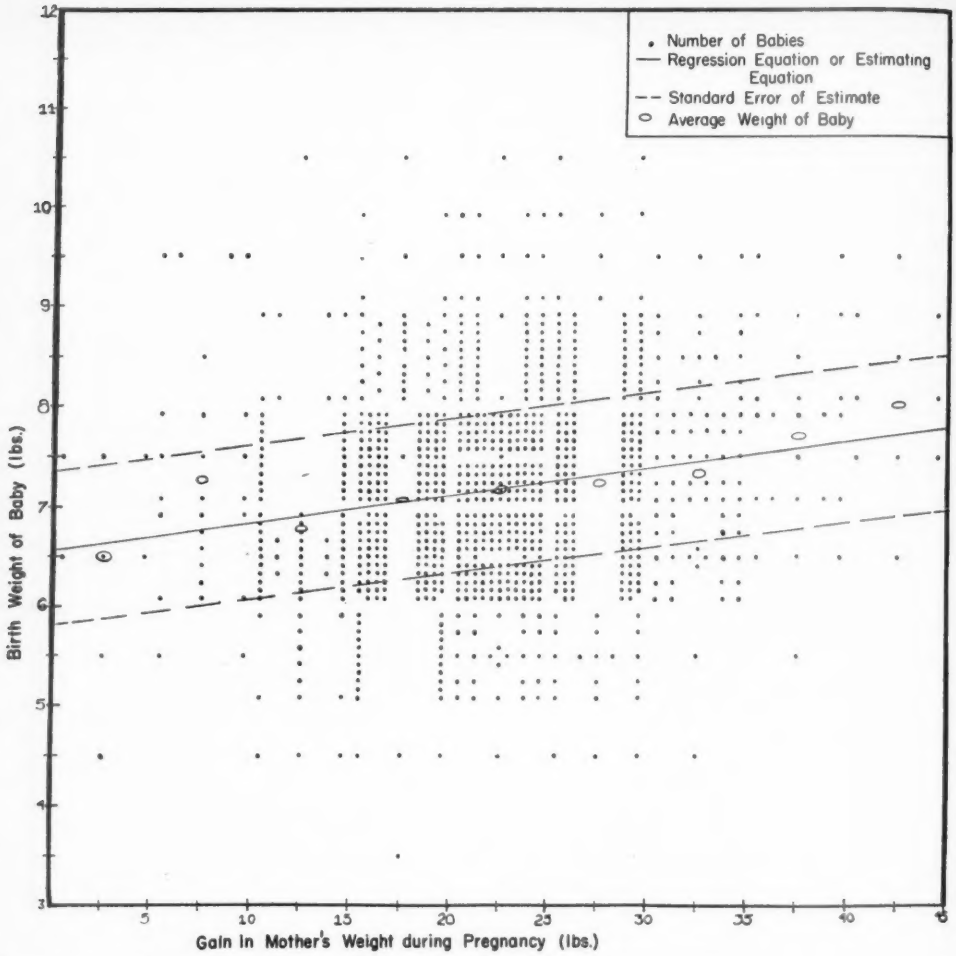
Table I shows the distribution of 979 cases according to mothers' gains in groups of 5 pounds ranging from 0 to 40 pounds and over. Each group contains the average weight of the newborn infant, the number of babies, male and female, and the average of both groups.

The table indicates that there is a progression in the increase of the average weights of the newborn infant. This parallels the mothers' gains during pregnancy. There is one exception, representing 26 cases of the group of mothers' gains 5 to 10 pounds. This correlation does not follow when comparison is made with male and female separately.

Fig. 1 contains the pertinent data of Table I and illustrates graphically the relationship between mothers' gains and weight of the babies at birth. The base line represents the gain of weight of mothers in 5-pound class intervals; the vertical axis, the weights of babies; each dot represents one case and there are 979 cases charted. The circles indicate the average weight of the babies of each group of mothers' gains. The average gain in weight of the mother, which is 22.28 pounds, and the average weight of the baby, 7 pounds, 3 ounces seem to fall in the same class interval.

The solid black line representing the line of the estimating equation and the broken lines representing the plus and minus variation of the standard error of estimate were derived by mathematical formulas. The plus and minus variation was found to be 0.9 pounds.

It would indicate that every 1-pound gain in mother's weight is accompanied by 0.25 pound increase in baby's birth weight. There is a 68 per cent probability that when a baby's birth weight is estimated from mothers' gain in weight, the actual baby's weight will fall within the plus and minus 0.9 pounds of the estimated value.



Graph I RELATIONSHIP OF MATERNAL WEIGHT-GAIN & WEIGHT OF NEWBORN

Fig. 1.

Analysis of Fig. 1

r = Coefficient of correlation = · 184928
r^2 = Coefficient of determination = · 034198 expressed in a percentage
Yc = Estimating equation = 6.636317+ · 025154 x
Sy = Standard error of estimate = · 910803
x = Mother's gain in weight during pregnancy
y = Baby's birth weight

R^2, the coefficient of determination represents the percentage of the original variability in "y," that is attributable to the influence of "x" on "y" when it is assumed that that influence is linearly exerted.

Knowing the gain on the mother's weight, the *estimating equation* makes it possible to estimate the birth weight of the baby. Naturally a question arises concerning the accuracy of the estimate—this is answered by the *standard error of estimate* (Sy), on the following terms:

Yc ± 1 Sy—has a 68.26 per cent probability of including the actual y
Yc ± 2 Sy—has a 95.45 per cent probability of including the actual y
Yc ± 3 Sy—has a 99.73 per cent probability of including the actual y

The foregoing is based on the assumption that both x and y are normally distributed. To illustrate the foregoing—assume that the mother's gain in weight was 30 pounds. Substituting this for x in the estimating equation, we have Yc = 6.6363 + .0252(30). Therefore Yc = 7.3909. Thus we would estimate the baby's weight as 7.39 pounds. The standard error

of estimate is .9108 pounds, therefore there is a 68 per cent probability that the baby's weight will fall within the limits of 7.3909 pounds ± .9108 pounds. That is, between 6.4801 and 8.3017 pounds. Similarly there is a 95 per cent probability that the baby's weight will fall between the limits of 7.3909 + 2(.9108) or 7.3909 ± 1.8216 or specifically between the 5.5693 and 9.2125 pounds. In similar fashion there is a 99.73 per cent probability that the baby's weight will fall between 4.6585 and 10.1233 pounds.

Significance of $r = .184929$

It is practically certain that the population r fell within the limits—.184928 ± .095928, or + .089000 to +.280856.

Therefore the hypothesis that a sample r of .184928 obtained from a sample of 979 observations could have been obtained from an uncorrelated parent population must be rejected. This sample r is definitely significant!

Stander and Pastore[8] considered the mother's gain per se of slight significance. They believed that specific weight change, expressed in percentage, was the true index of the mother's gain. This was capable of comparison with norms established by them for small (40 kg.), medium (60 kg.), and large (80 kg.) women. Their curves of weight change during pregnancy would indicate that the heavier the patient, the more marked was her gain. Bray,[9] in reviewing the literature, notes that a number of observers reported that heavy women gained more than light women. The results of his studies failed to substantiate earlier opinions that body build had an effect upon the increase of weight during pregnancy. Only McIlroy and Rodway[5] showed the reverse, namely, that heavy patients showed less gain in weight than those of lighter build. Four of their patients who failed to gain weight were large women weighing over eleven stones* (154 pounds).

It has long been generally believed that large women gain more during their pregnancy and tend to bear heavier babies. To test these statements we have grouped the extremes in weights of our cases, those weighing 100 pounds or less, and 175 pounds or more, before pregnancy. The results are indicated in Tables II and III.

TABLE II. COMPARISON OF MOTHER'S GAINS AND WEIGHTS OF BABIES OF TOTAL AND SPECIAL MOTHER-WEIGHT GROUPS

GROUP	AVERAGE MOTHER'S GAIN IN POUNDS	AVERAGE WEIGHT OF BABY (LB.)	(OZ.)	BABIES (NO.)	MALES (NO.)	FEMALES (NO.)	AVERAGE WEIGHT OF MALE (LB.)	(OZ.)	AVERAGE WEIGHT OF FEMALE (LB.)	(OZ.)
A*	22.28	7	3	979	507	472	7	5	7	
B†	23.13	6	9	26	11	15	6	7	6	11
C‡	19.25	8		40	19	21	8	2	7	15

*Group A represents total of 979 cases.
†Group B includes mothers weighing 82 to 100 pounds before pregnancy.
‡Group C includes mothers weighing 175 to 252 pounds before pregnancy.

1. The average gain in light women was greater than that of the entire group.

2. The average gain in heavier women was less than that of entire group and that of light women.

3. The average weight of baby was greater in heavier women than the weight of the entire group and light women.

Two facts are suggested by Tables II and III, namely:

1. The gains during pregnancy of heavier women are not greater than those at the other extreme in weight.

2. Heavier women tend to bear heavier babies.

*Stone is equivalent of 14 pounds.

Table III shows a comparison of babies' weights of light and heavy women with similar gains during pregnancy.

TABLE III. RELATION OF MOTHER'S GAIN AND WEIGHT OF BABY IN SPECIAL GROUPS OF MOTHER'S WEIGHTS BEFORE PREGNANCY

GROUP B MOTHERS WEIGHING 82 TO 100 LB.				GROUP C MOTHERS WEIGHING 175 TO 252 LB.			
MOTHER'S GAINS IN POUNDS*	AVERAGE WEIGHT OF BABY (LB.)	(OZ.)	BABIES (NO.)	MOTHER'S GAINS IN POUNDS*	AVERAGE WEIGHT OF BABY (LB.)	(OZ.)	BABIES (NO.)
0 to 5				0 to 5	7	8	2
5 to 10				5 to 10	7	13	3
10 to 15	7	8	1	10 to 15	8	6	7
15 to 20	6	6	7	15 to 20	8	5	10
20 to 25	6	5	8	20 to 25	8	6	8
25 to 30	6	15	7	25 to 30	7	13	6
30 to 35	6		2	30 to 35	8		2
35 to 40	6	8	1	35 to 40	8	8	2

*0 pounds up to but not including 5 pounds, etc.

Summary and Conclusion

The relationship between mother's weight gain and the weight of the baby at birth has been examined from the data of 979 parturient cases. The average mother's gain was 22.28 pounds; the average weight of the baby was 7 pounds, 3 ounces.

There is correlation between the weight gain of the mother and the weight of the baby at birth. Although the degree of correlation is low, it is nevertheless significant. There is a 68 per cent probability that the baby's birth weight can be predicted on the basis of the mother's gain, within a range of plus or minus 0.9 pound of the estimated figure.

The size of the mother influences the weight gain during pregnancy. The light women show a larger gain. The heavier women show a smaller gain than the light. Heavier women tend to bear heavier offspring.

We are indebted to Harold Stein, B.S.S., M.B.A., Instructor in Economics, Brooklyn College, Brooklyn, N. Y., for assistance in the statistical analysis.

References

1. Davis, C. H.: AM. J. OBST. & GYNEC. 6: 575, 1923.
2. Slemons, J. H., and Fagan, R. H.: AM. J. OBST. & GYNEC. 14: 159, 1927.
3. Bingham, A. W.: AM. J. OBST. & GYNEC 23: 38, 1932.
4. Hanley, B. J.: West. J. Surg. 42: 251, 1934.
5. McIlroy, A. L., and Rodway, H.: J. Obst. & Gynaec. Brit. Emp. 44: 221, 1937.
6. Cummings, H. A.: AM. J. OBST. & GYNEC. 27: 808, 1934.
7. Toombs, P. W.: AM. J. OBST. & GYNEC. 22: 851, 1931.
8. Stander, H. J., and Pastore, J. B.: AM. J. OBST. & GYNEC. 39: 928, 1940.
9. Bray, Philip, N.: AM. J. OBST. & GYNEC. 35: 802, 1938.

FATAL HEMORRHAGE FROM AN ANGIOMATOUS POLYP OF ILEUM COMPLICATING PREGNANCY

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THE literature to date contains reports of approximately 93 cases of angioma of the gastrointestional tract. The most masterful review of the subject was written by Kaijser[1] in 1936. For a complete bibliography up to that time the reader is referred to his publication. Kaijser collected and classified in table form 74 cases of angioma of the gastrointestinal tract, of which 8 occurred in the ileum. In 1940 Pierose[2] reviewed the cases which had been published since Kaijser's review, and reported a case of his own, bringing the total to 84. Since then, cases reported by Hunt,[3] Morton,[4] White,[5] Stajano,[6] Gladden,[7] and Christopher[8] have brought the complete total to date to 93. Of these, in about 13 cases, the lesion occurred in the ileum. In most of these, the angioma was one of several similar lesions coexisting in other segments of the intestines, especially in the jejunum. In very few of these instances was the lesion solitary and limited to the ileum. Kaijser, in his discussion, emphasized the desirability of reporting every case in order to amplify our knowledge of the condition. The case reported in this publication presents a feature which, as far as the author could determine, was not present in any of the previously reported cases, and hence the only one of its kind in the literature to date. It was therefore considered worthy of publication.

Case Report

M. C., aged 26 years, Irish-American housewife, 6 months pregnant, was admitted to the Prospect Heights Hospital on Sept. 3, 1943, suffering from severe secondary anemia which resulted from repeated attacks of rectal bleeding. The bleeding episodes began in February, 1942, six months following her first pregnancy, and had become worse with the onset of her present pregnancy.

The patient's past history disclosed that she had had scarlet fever in childhood and Bright's disease thirteen years ago. About seven years ago, her tonsils were removed. Menses began at the age of 15 years and were irregular and prolonged, each period lasting about seven days. Her first pregnancy terminated in a full-term stillbirth on December 14, 1941. It was believed to be due to a complicating hypertension with edema. This condition, however, subsided post partum. At that time she also had a marked anemia, the red cell count having been 3,690,000 per cubic millimeter and the hemoglobin 43 per cent (Newcomer).

On admission to the hospital her pulse was 70 and respirations 23 per minute. The temperature was normal. She showed all the signs and symptoms of an extremely severe anemia. There was a distinct hemic murmur. The abdomen showed an enlarged uterus corresponding to six months' gravidity. There was active bleeding per rectum, where a mass was allegedly palpable at the ampulla recti.

The laboratory data was as follows:

Blood Count:

Red blood cells— 1,570,000 per c.mm.
Hemoglobin — 30 per cent (Newcomer)
White blood cells— 9,250 per c.mm. of which 88 per cent were polynuclear cells and 12 per cent lymphocytes.

Blood grouping tests showed her to be a group O, Rh positive.
Blood chemistry showed a creatinine of 1.8 mg. per cent.

Urinalysis was essentially normal. The specific gravity was 1.038, reaction acid, faint trace of sugar, albumin and acetone negative. The sediment consisted of an occasional red blood cell and about 5 white blood cells per high-power field.

The patient was given intravenous glucose and saline and treated for impending shock. During the night, the nurse reported that the fetal heart sounds could not be heard. While preparations were being made for a blood transfusion, a massive hemorrhage per rectum occurred, and the patient expired before the blood transfusion could be performed.

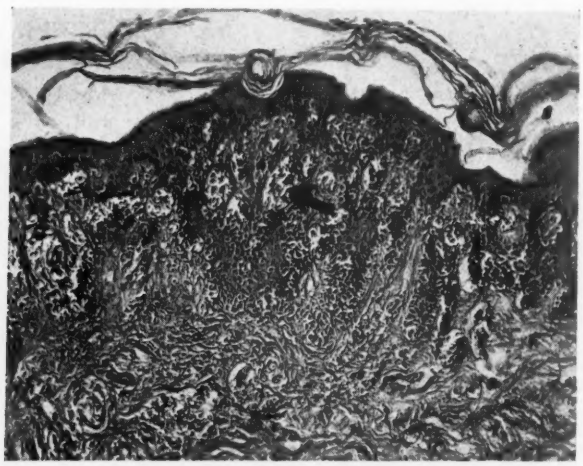

Fig. 1.—Photomicrograph of skin nevus from foot, showing the ovoid clusters of pigmented nevus cells (arrow) in papillae of cutis, lying between deeply pigmented rete pegs (×130).

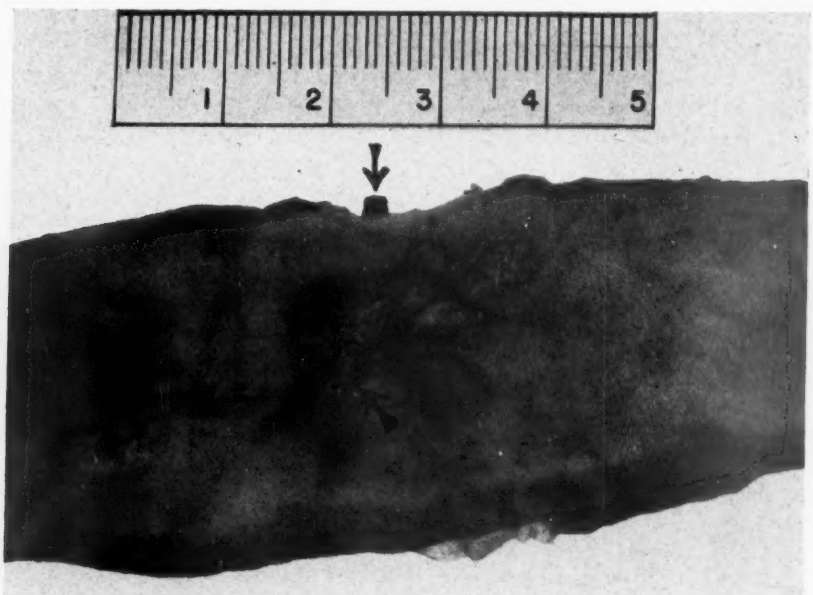

Fig. 2.—Gross specimen of opened ileum showing mucosal surface with area of ulceration and angiomatous polyp projecting into the lumen. Note blood clot covering free end of polyp (arrow). The arrow between ruler and ileum shows the mesenteric artery (from which the angioma arises) entering the wall of the gut.

Postmortem Examination.—General description: The body was that of a fairly well-developed and well-nourished young white woman. The skin and mucous membranes were pale. There was a generalized subcutaneous pitting edema of the extremities. There were numerous brown to blue-black pigmented flat nevi, diffusely scattered over the entire skin, and especially marked on the legs and feet. The microscopic examination of these nevi showed them to be of the benign pigmented type (Fig. 1).

Cavities: The pleural, pericardial and peritoneal cavities were normal.

Cardiovascular system: The heart weighed 225 grams. It was essentially normal except for microscopic evidence of a mild degree of myocardial degeneration.

Respiratory system was entirely normal.

Gastrointestinal system was normal down to a point in the ileum about 50 cm. above the ileocecal junction. From this point down to the rectum the intestines were distended with fluid and clotted blood which was visible through the wall of the gut. Near the upper level of the column of blood, a mesenteric vessel of relatively large caliber was found entering the wall of the ileum and leading to an area of superficial ulceration in the mucosa, about 1.5 cm. in greatest dimension. From the center of this ulcerated area there projected a soft, polypoid structure about 0.8 cm. in length, and covered with fresh blood clot (Fig. 2). The mucosa surrounding the base of the polyp showed a finely nodular thickening.

Fig. 3.—Low-power magnification of ileum at site of polyp. Note the large caliber of the artery (*A*) as it courses through the wall of the gut to the mucosa where it branches (*A'*) out to form the angiomatous polyp (*B*). The thrombotic mass (*C*) which covered the free end of the polyp has been detached. (×10.)

Microscopic section of this portion of ileum showed the mesenteric vessel entering the wall to be of a relatively large caliber throughout its course. (Fig. 3). Within the wall of the ileum it divided into branches which formed congeries of vessels, assuming the characteristic architecture of capillary angiomas. These lesions were found in the serosal, muscular, and mucosal layers. In the latter they gave rise to the polyp described in the gross. The polyp was composed of numerous blood capillaries, the endothelial cells of which were hyperplastic and large. It had penetrated the mucosa and showed a secondary inflammatory process with ulceration of its surface. Here it was partly covered with fresh thrombus deposits, the major portion of which had been detached during the gross examination of the specimen (Fig. 4). Some of the angiomas within the wall of the ileum occurred as discrete nodules which invaginated into the sinuses lined by hyperplastic endothelial cells. In areas the degree of endothelial proliferation in the capillaries was so pronounced as to suggest a possible angio-endotheliomatous change (Fig. 5). There was, however, no definite evidence of malignancy in any of the angiomas. Throughout the submucosa, as well as in the muscularis and serosa, were found numerous dilated but empty sinuses which distorted the normal architecture of those areas, forming huge gaps between muscle bundles and between submucosa and muscularis.

The rest of the gastrointestinal tract, including the appendix, mesentery, and omentum were essentially normal. The pancreas weighed 60 grams and showed no changes.

Biliary system: The liver weighed 1,480 grams and showed no changes. The gall bladder, cystic duct, common duct, and ampulla of Vater were normal.

Urinary system: The right kidney weighed 120 grams and the left kidney 105 grams. They were normal. The ureters, bladder, and urethra were normal.

Genital system: The external genitalia were normal. The uterus contained a normally developed dead female fetus of six months' gestation. The placenta was normally implanted and showed no changes. The umbilical cord was normal. The myometrium was very pale and edematous. The Fallopian tubes and ovaries were normal.

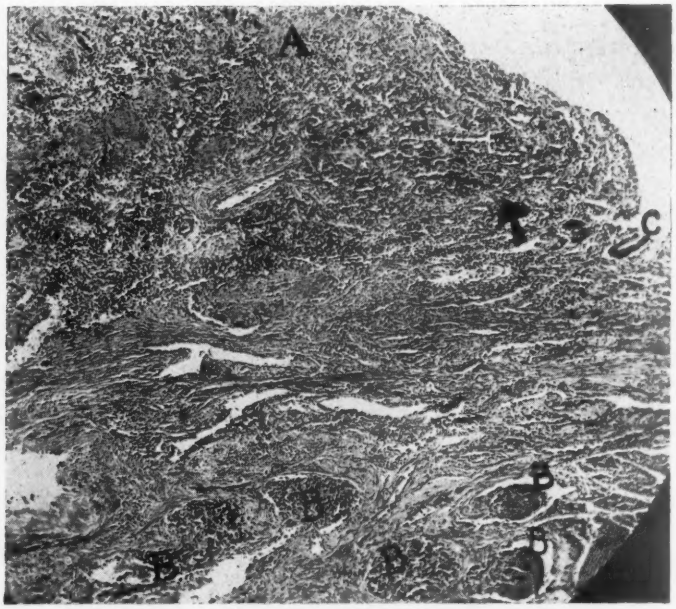

Fig. 4.—Section through the polyp (*A*) including underlying wall with its capillary angiomas (*B*) and ulceration of the mucosal lining (*C*). Note the myriads of capillaries in the polyp and the inflammatory infiltrate within it (arrow). (×70.)

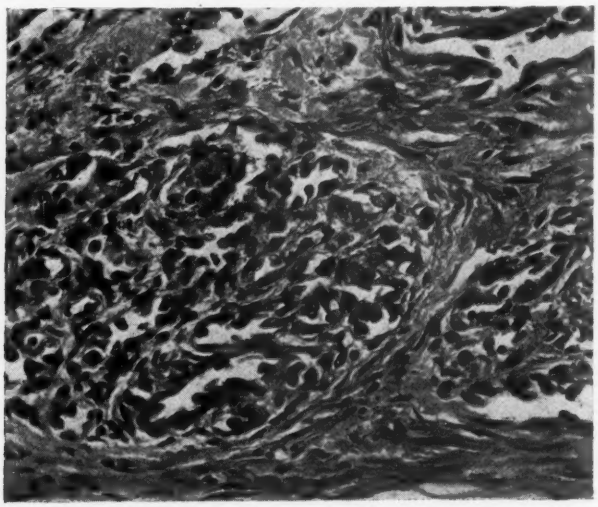

Fig. 5.—Higher magnification of the angiomas in the wall of the ileum shown in Fig. 4. Note the marked endothelial proliferation of the capillaries of the angiomas and the endothelium-lined spaces in which they are found. (×300.)

Lymphatic system: The thymus weighed 12 grams and showed no changes. The spleen weighed 140 grams and showed hypertrophy of follicles. The sinuses were almost completely devoid of blood. A small splenulus in the gastrolienic ligament showed similar changes.

Anatomic Diagnosis:

1. Angiomatous polyp of ileum, with ulceration and hemorrhage.
2. Massive intestinal hemorrhage.
3. Secondary anemia.
4. Subcutaneous edema.
5. Gravid uterus (six-month female fetus).
6. Follicular hyperplasia of spleen and splenulus.
7. Multiple benign pigmented nevi of skin.

Discussion

Detailed discussion of the general subject will not be attempted here. This was already admirably done in the publications previously mentioned. A few of the more pertinent facts will be mentioned in relation to the present case. Bleeding vascular lesions of the gastrointestinal tract may be due to telangiectasia (local or as an expression of a general diathesis), varicosities, or true neoplasms. The latter include cavernous angioma, capillary agioma, and angioendothelioma. Grossly the lesions may manifest themselves in the form of ulcers (the polyp may be unnoticed), fungating bulky masses projecting into the lumen, or strictures. The present case is one of a true neoplasm involving all layers of the portion of ileum affected. In fact, in some sections, as was already indicated above, the neoplasm assumed features suggestive of an endothelioma which is a malignant lesion. The process was a local one, no other angiomas having been found elsewhere. At this point it may be of interest to note that there was a marked tendency to nevus formation in the skin. This may have some relationship to the capillary angioma in the ileum, since many of the skin nevi are capillary angiomas. Clinically it was noted that the pigmented nevi of the skin became more accentuated and increased in number with pregnancy. It is conceivable that the state of gravidity activated the angioma as well as the skin nevi. Kaijser makes mention of the fact that in one of his cases of angioma of the stomach, bleeding increased with puberty, and he mentioned puberty and gravidity among the endogenous stimuli which may activate the development of angiomas. He also cites, as a case in point, the case of Blaschko's in which the angioma followed pregnancy.

The fact that in this case the lesion complicated pregnancy makes it unique and adds to its importance. No other such instance has been found in the literature. It is quite probable that intestinal bleeding due to an angioma of the tract occurs more commonly in pregnancy than is supposed, but is overlooked because the bleeding is inconsequential and ceases with termination of the pregnancy. It will be noted that in this case the patient's previous pregnancy (about two years prior to the recent one), terminated in a stillbirth, the patient showing a profound anemia at the time, with a hemoglobin of only 43 per cent. It is quite likely that she had had intestinal bleeding episodes with the first pregnancy also, but they probably went unnoticed because they were not massive enough to attract her attention, and the absence of vaginal bleeding probably gave her physician a false sense of security, so that more strenuous efforts to determine the cause of the anemia were not made.

The matter of diagnosis, naturally, is of prime importance, since recent experiences have shown that the condition is amenable to surgery and cure, if the lesions are not too diffuse or multiple.[2, 5, 8] In some instances x-ray may be of aid in diagnosis,[9] but even in the absence of positive x-ray findings, unexplained intestinal bleeding of a degree sufficient to produce an anemia should be considered a definite indication for exploratory laparotomy to exclude an

operable angioma of the intestines. In this case, as has been found to be also true in others, the large offending artery shown in the specimen could serve as a guide to the location of the lesion, and the level of the blood in the lumen of the gut, visible as it was through the wall, could indicate the source of the bleeding. Although, in the present case, surgical intervention was impossible upon admission to the hospital, because of the massiveness of the hemorrhage, it is possible that had the diagnosis been made earlier in her course, surgery might have spared her life.

Summary

1. A unique case of fatal hemorrhage from an angiomatous polyp of the ileum complicating pregnancy is reported. No similar case complicating pregnancy was found in the literature.

2. A brief review of the subject of angioma of the gastrointestinal tract reported to date shows a total of 94 cases including the author's case. Of these, only about 13 cases involved the ileum, most of them being cases in which coexisting angiomas were found in other segments of the intestine, especially jejunum. Instances of solitary angiomas of the ileum alone, as in the author's case, are even rarer.

3. A plea is made for early diagnosis of the condition and attempt at surgical intervention.

References

1. Kaijser, R.: Arch. f. klin. Chir. **187**: 351, 1936.
2. Pierose, P. N.: J. A. M. A. **115**: 209, 1940.
3. Hunt, V. C.: Surgery **10**: 651, 1941.
4. Morton, C. B., and Burger, R. E.: Surgery **10**: 891, 1941.
5. White, R. J.: South. Surgeon **10**: 886, 1941.
6. Stajano, C.: Arch. urug. de med., cir. y especialid. **19**: 466, 1941.
7. Gladden, J. R.: Am. J. Surg. **56**: 495, 1942.
8. Christopher, F.: Ann. Surg. **116**: 945, 1942.
9. Weber, H. M., and Kirklin, B. R.: Am. J. Roentgenol. **47**: 243, 1942.

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COCCIDIOIDAL PELVIC INFLAMMATORY DISEASE

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INFECTION of the female genital tract with *Coccidioides immitis* has been recorded once before.[1] In both cases, surgery has been followed by complete recovery. While Jacobson attributed the recovery of his patient to the use of a coccidioidin vaccine and colloidal copper, ours has regained her health with no "specific" therapy.

Case Report

Mrs. G. L., aged 33 years, entered the Alameda County Hospital on Aug. 30, 1941, complaining of severe lower abdominal pain and fever.

The only significant points in her past history were concerned with her activities in an area known to be endemic for coccidioidomycosis. She had lived only in Portland, San

Francisco, and Los Angeles until 1936, when she began to take annual trips to Tucson, Arizona, where she camped in the surrounding desert country digging for archeological ruins. She was in excellent health until, on one of these trips in 1939, she had a brief illness consisting of nausea, vomiting, and weakness for two weeks. A tubal insufflation was done at this time because of sterility and she was told that her tubes were open.

She remained in Arizona, and her health was good until April, 1941 (four months before entry), when she had pelvic pain, chills, fever, and malaise which persisted for several weeks. These symptoms abated, but six hours before admission, she was awakened by severe lower abdominal pains accompanied by vomiting.

Upon admission, the patient appeared pale, undernourished and in obvious distress, with a temperature of 103.6° F. and a pulse rate of 130. The only pertinent findings were made on pelvic examination. The lower half of the abdomen was distended, rigid, and tender to light touch. The uterus seemed to be of average size and there were ill-defined tender masses in both adnexal regions. The hemoglobin was 9.6 Gm. (57 per cent), red blood cell count was 3,460,000, and leucocyte count 13,200 with 78 per cent neutrophiles. The blood sedimentation rate showed a drop of 18 mm. in 11 minutes.

The initial diagnosis was bilateral salpingo-oophoritis and pelvic peritonitis of undetermined etiology. She continued to have a high swinging fever for ten days despite intensive sulfathiazole therapy. A colpotomy was done because of a fluctuant abscess bulging into the cul-de-sac, and a large quantity of greenish pus escaped. This was negative for gonococci on smear and culture, and a guinea pig inoculation was reported after one month as "negative for tuberculosis."

During the next two months, she remained in the hospital with an intermittent fever, a moderate anemia, persistent leucocytosis, and a rapid sedimentation time. On two occasions, the colpotomy wound was reopened because of accumulated purulent material in the cul-de-sac. Sulfathiazole was again administered in two-week courses twice but with no evident influence upon the course of the infection. Finally, on Jan. 7, 1942, she was dismissed with relative freedom from pain and no fever. Because of the repeated exacerbations and the persistence of bilateral tuboovarian masses, she was asked to return for surgery after two months of rest.

On March 1 a laparotomy was performed and the entire visceral and parietal peritoneum was found to be studded with small, white irregular nodules varying from 1 to 3 mm. in size. The appearance of the abdomen and pelvic organs was like that of advanced tuberculous peritonitis. The uterus was slightly enlarged and covered with adhesions. The left tube and ovary were involved in a single cul-de-sac mass, 8 cm. in diameter and containing multilocular abscesses. The right ovary appeared normal, but the right tube was markedly inflamed and thickened, sealed at the fimbriated end, and contained a brown fluid. The left ovary and both tubes were removed and a subtotal hysterectomy was done.

The pathologic report was submitted by Dr. M. R. Oldt. On microscopic examination, the abscess walls consisted of granulation tissue densely infiltrated with plasma cells and occasional eosinophiles and containing tubercle-like lesions composed of epithelioid cells and giant cells of Langhans' type. Sections from the right tube (Figs. 1 and 2) and from the peritoneum showed similar lesions. The involved areas contained globular bodies 50 to 60 micra in diameter with double peripheral membranes. Some of the organisms were filled with endospores. Diagnosis: Coccidioidal granuloma of tubes, ovary, and peritoneum.

The patient had a smooth, afebrile convalescence. Hospitalization was prolonged because of a small draining sinus at the lower angle of the incision. Cultures taken from this sinus, and also from the posterior vaginal fornix showed a growth of *Coccidioides immitis*. Roentgenograms of the chest revealed no lesions or evidence of scarring, and no bony lesions were seen in x-rays of the pelvis.

Coccidioidin skin tests performed five and seven weeks postoperatively were positive in 1:100 dilution, negative in 1:1,000 dilution. Three complement fixation tests on serial dilutions of serum were done during the second month postoperatively, and all were positive through the 1:32 dilution and negative with 1:64 dilutions.

At three, four, and five months after surgery, examinations showed no masses or tenderness in the pelvis and the patient had no complaints. The abdominal and colpotomy wounds healed, and she gained 20 pounds in weight. Her temperature, leucocyte count, and sedimentation rate have remained normal. Ten months after surgery, the serum complement

fixation test was positive in 1:8 dilution and negative in 1:16 dilution. This reduction in titer indicated that the infection was diminishing and coincided with known clinical improvement.

Eighteen months and again two years after surgery, examinations showed normal findings except for a very slightly enlarged but nontender right ovary. Coccidioidin skin tests were repeated with the same results as on the previous examinations. She was now 10 pounds overweight, was working full time in a manufacturing plant, and stated that her general health was excellent.

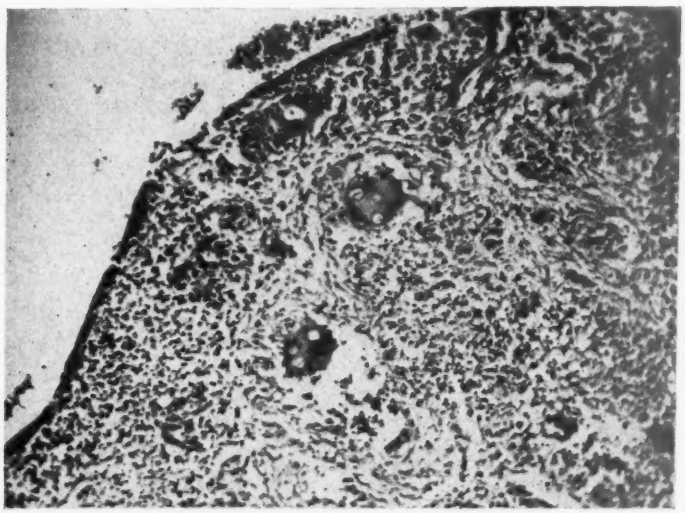

Fig. 1.—Wall of right tube (×120) showing tubercles containing *Coccidioides immitis* in giant cells.

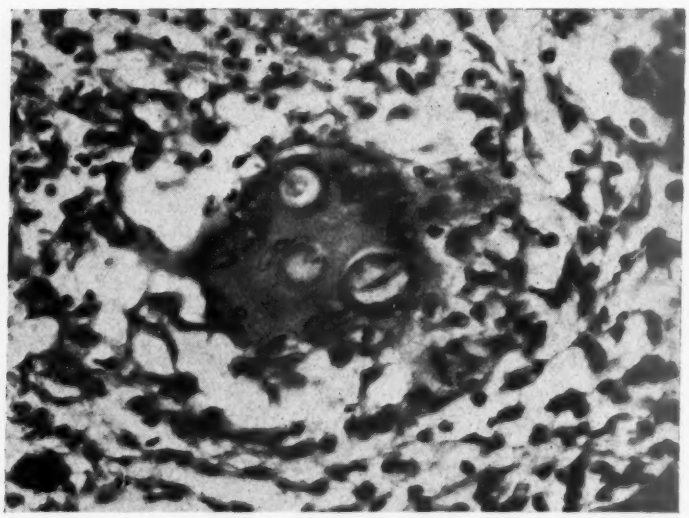

Fig. 2.—Details of a giant cell (×500) containing three organisms.

Comment

Except for occasional primary skin lesions, the initial route of infection is by inhalation of the coccidioidal chlamydospores which inhabit the soil of certain dry areas in the Southwest. The region near Tucson, Arizona, is known to be an endemic focus[2] and it is highly probable that this patient acquired her infection while digging ruins in the neighboring desert, at least six months before entry to the hospital. Whether the tubal insufflation had any part in the inoculation or spread of the disease is problematical.

The initial infection is commonly mild, and it has been estimated that only once in 500 to 1,000 cases does the fungus disseminate in this manner.[3] That coccidioidal peritonitis itself is unsual is indicated by a report in 1939[4] of the second case in which the diagnosis was made during life. The infection occurred in a man who died one month later.

The precise factors which determined the favorable outcome in our case are not known. It is very unlikely that the administration of sulfonamides influenced the course of her illness. Surgical extirpation of the heavily infected pelvic organs undoubtedly favored recovery, but her immunologic defense must have been high at that time.

Summary

A case is reported of disseminated coccidioidomycosis involving primarily the uterus, tubes, and one ovary. Surgical removal of these organs was followed by a complete cure.

Appreciation is expressed to Dr. C. E. Smith and Miss R. J. Wheatlake of the Department of Public Health and Preventive Medicine, Stanford University School of Medicine, for their assistance in the coccidioidin and serologic tests; and to Miss Ida May Stevens, Supervising Morbidity Statistician, Bureau of Epidemiology, for her review of the coccidioidal granuloma cases reported to the California State Department of Public Health.

References

1. Jacobson, H. P.: M. J. & Rec. **130**: 424, 1929.
2. Farness, O. J.: J. A. M. A. **116**: 1749, 1941.
3. Smith, C. E.: M. Clin. North America **27**: 790, 1943.
4. Ruddock, J. C.: J. A. M. A. **113**: 2054, 1939.

GONORRHEAL ARTHRITIS COMPLICATING PREGNANCY TREATED WITH PENICILLIN

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GONORRHEAL arthritis in women is relatively rare. Salberg and Brunet reported (1940) that in the Women's Division of the Public Health Institute of Chicago only thirty cases were observed in the years from 1931 to 1938, an incidence of 1 in 200 of the women treated for gonorrhea. Gonorrheal arthritis appears to be an extremely rare complication of pregnancy, or at least one that has rarely been reported in the literature. Few textbooks on obstetrics mention this complication; Royston, in 1923, reported four cases of gonorrheal arthritis during pregnancy; de Sa Peretra, Urvald, in 1936, reported a very severe case of gonococcic polyarthritis and discussed the efficacy of vaccinotherapy; Upton, 1938, added another case report with a discussion of the general problem; and Mengert and Paul, 1942, reported the cure of three cases late in pregnancy in a discussion of the effects of artificial pyrexia on pregnant women. The case to be reported appears to be the first treated with penicillin.

Case Report

Mrs. R., a para ii, who had a difficult first labor, was referred to me during her seventh month of pregnancy. My original examination was negative except for the presence of polyps in the cervix. On June 8,

1944, she reported at the office complaining of very severe pain in her right arm, and she was sent to the Delaware Hospital for observation. On admission, her temperature was 99.6° F., but thereafter it was normal. Her history taken at the time indicated that she had a slight vaginal discharge but there were no symptoms suggestive of gonorrhea. Neither smears nor cultures were made at this time. On the third day she was permitted to return home under the care of her family physician who started large doses of vitamin B. A diagnosis of neuritis was recorded on the hospital record. On July 5 she was seen at my office, but the skin of the wrist was so badly blistered from the use of tincture of iodine that an examination was not possible. She was next seen on July 20, when it was found that she had a marked deformity of the right wrist. She was sent back to Delaware Hospital for x-ray examination and treatment. Dr. Lattomus found: "Advanced decalcification of the carpal bones with destruction of many of the articulating surfaces; this is particularly true of the distal articulating surfaces of the radius. There is a dorsal subluxation of the ulna. Diagnosis: Infectious arthritis. Gonorrhea should be ruled out."

Fig. 1.—The wrist, on July 20, 1944, showed marked decalcification and destruction of many of the articulating surfaces. There was a dorsal subluxation of the radius shown on a lateral plate.

The original smears were negative but the gonococcus was grown in the cultures. As soon as the diagnosis of gonorrheal arthritis was established, 20,000 units of penicillin were administered intramuscularly five times daily until she had a total of 1,000,000 units. Smears taken after 500,000 units were negative, and a culture after 600,000 units was negative. On admission to the hospital the wrist was supported with a light plaster splint which permitted free movement of the fingers. Within a few days the swelling and pain disappeared and the patient was permitted to move her wrist freely. A blood-calcium determination

made on July 22 showed only 8.5 per cent, and thereafter she was given 60 grains daily of dicalcium phosphate compound with viosterol. It is possible that this aided in her recovery. She went into labor spontaneously on Aug. 7, 1944. The labor and puerperium were uneventful. Her temperature remained under 99° F. during her entire stay in the hospital. Re-examination of the involved wrist two days before she left the hospital showed "complete disappearance of the infectious process. Many of the articulating spaces are still preserved. There is, however, a destruction of the distal articulating surface of the radius with the same dorsal displacement of the ulna as seen in the examination of July 20, 1944." The patient now has a very serviceable wrist but there is still the same displacement of the ulna.

Fig. 2.—The wrist, on August 14, just before discharge from the hospital, showed a complete disappearance of the infectious process and a considerable degree of restoration with preservation of many of the articulating surfaces.

Discussion

Gonorrhea is such a rare finding among my private patients that I did not suspect that it was the cause of the trouble in this case. However, after the diagnosis was made, the husband admitted that he was under treatment for an infection. Furthermore, the smears were all negative and it was only through the cultures that the x-ray diagnosis was established as correct. The x-ray findings in gonorrheal arthritis seem to be quite typical and this aid should be obtained whenever a painful joint develops.

A review of the cases reported in the literature indicates that gonorrheal arthritis is most likely to develop during the third trimester of pregnancy. The arthritis also develops usually during the subacute or chronic stage of the local infection rather than during the acute stage.

Gonorrheal arthritis may be monoarticular or polyarticular. It has been stated that the gonococcus has a predilection for the upper extremi-

ties in women and for the lower ones in men. In the thirty cases reported by Salberg and Brunet, the joints attacked were: wrist, seven cases; knee, wrist, one case; shoulder, wrist, two cases; shoulder, foot, one case; shoulder, hand, one case; shoulder, wrist, ankle, one case; knee, ankle, two cases; knee, wrist, two cases; knee, finger, toe, one case; foot, wrist, two cases. The wrist alone or with other joints were involved fifteen times, or in one-half of all cases.

Mengert and Paul have demonstrated that artificial pyrexia may be used safely during pregnancy for the treatment of arthritis. Use of large doses of sulfonamides during pregnancy does not appear rational owing to the known toxicity of these drugs. Penicillin promises prompt cure of gonorrhea without any apparent untoward effects. The seriousness of gonorrheal arthritis complicating pregnancy would seem to justify using a dose of penicillin large enough to insure a cure. It is probable that a smaller dose than the one used in this case would have been adequate.

References

Royston, G. D.: Am. J. Obst. & Gynec. 5: 512, 1923.
de Sa Peretra, Urvald: Hospital, Rio de Janeiro 8: 889, 1936.
Upton, J. R.: California & West. Med. 48: 326, 1938.
Salbert, J. B., and Brunet, W. M.: M. Rec. 152: 294, 1940.
Mengert, W. F., and Paul, W. D.: Am. J. Obst. & Gynec. 44: 702, 1942.

REDUCING PROPERTIES OF THE CHORIONIC GONADOTROPIC HORMONE AS RELATED TO THE CHEMICAL DETERMINATION OF PREGNANCY

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Mello[1] has recently described a procedure for the chemical determination of pregnancy in which a urinary reducing factor which is assumed to be the chorionic gonadotropic hormone is separated from urine and is estimated by determining its ability to reduce a sugar reagent. Since the influence of urinary glucose was not described, an account of such observations may be desirable along with a brief discussion of earlier observations regarding reducing factors in relation to pregnancy determination.

Experimental

In the procedure described by Mello[1] the reaction of the urine is adjusted to pH 4 with acetic acid, and the reducing fraction is adsorbed on kaolin. After eluting with 0.1 N sodium hydroxide and centrifuging, the reducing power of the eluate is estimated by Somogyi's sugar method.[2] This is expressed in terms of the difference between a blank titer and the titer required by the eluate and is a measure of the reducing fraction derived from 1 c.c. of urine. Values obtained in this manner and exceeding 1.6 c.c. have been included in the range of a positive pregnancy reaction.

In the present study, varying amounts of glucose were added to nonpregnancy urine which was then treated according to this procedure. From the data presented in Table I it is apparent that small quantities of urinary glucose are sufficient to significantly alter the results. In this series the urine glucose appearing in the eluate varied between 7 and 40 per cent of the added sugar, this percentage gradually decreasing with an increase in the concentration in the urine. It may be observed that in this case the addition of 0.1 per cent glucose is sufficient to bring the total reducing fraction of the eluate within the range ascribed to pregnancy.

TABLE I. INFLUENCE OF URINARY GLUCOSE UPON THE RESULTS

AMOUNT OF GLUCOSE PRESENT (%)	REDUCING POWER PER C.C. OF URINE IN TERMS OF 0.005 N SODIUM THIOSULFATE (C.C.)
0.0	0.58
0.005	0.71
0.01	0.97
0.03	1.11
0.05	1.27
0.05	1.395
0.1	1.925
0.2	2.58
0.3	2.63
0.5	3.20

TABLE II. SUMMARY OF RESULTS WITH URINE SPECIMENS

		SPECIFIC GRAVITY	REDUCING POWER PER C.C. OF URINE IN TERMS OF 0.005 N SODIUM THIOSULFATE (C.C.)
Nonpregnancy	Average	1.024	1.54
	Maximum	1.045	3.45
	Minimum	1.006	0.20
	(Per cent false: 42)		
Pregnancy	Average	1.021	1.25
	Maximum	1.030	3.00
	Minimum	1.013	0.30
	(Per cent false: 38)		

Since this concentration of urinary reducing substances expressed as glucose is not unusual in normal urine, eluates were prepared from a number of such nonpregnancy specimens in order to determine whether such materials might interfere following the use of kaolin. It was found that in 42 per cent of fifty cases the reducing power of the prepared eluates was sufficient to exceed the limit ascribed to pregnancy. Such specimens gave a negative test with Benedict's qualitative sugar reagent. On the other hand, the variation in the reducing materials in fifty pregnancy specimens was sufficient to give values below that assigned to pregnancy in 38 per cent of fifty cases. It would therefore appear that the reducing agents present in normal urine are of sufficient magnitude and vary enough to seriously interfere with the use of the procedure.

Discussion

Since the use of a sugar reagent occurred to Mello after following some of our earlier studies on reducing factors as related to the determination of pregnancy, a brief discussion of some of these earlier findings and certain conclusions which have been drawn may be of interest. While dealing with carbohydrates in biologic solutions, it was observed by Visscher and Bowman that a characteristic type of precipitate, apparently not related to the presence of a simple carbohydrate, forms when pregnancy urine is treated under certain conditions with phenylhydrazine.[3] Following a brief account of these observations, numerous reports indicated that the correlation with pregnancy is not sufficient to warrant its use as a test.[4-9] On the other hand, others reported that with certain precautions considerable accuracy could be obtained.[10-14] A gradual decline in the reaction following delivery was reported[13] and positive reactions were observed with added gonadotropin.[11-13]

Frech applied the reaction in 513 cases in one series and reported about 92 per cent accuracy;[14] however, in a subsequent series he obtained a much lower percentage of correct results.[15] Our own experience in part parallels that of Frech. In a second laboratory employing new reagents and known specimens,

it immediately became apparent that there was marked contrast between this second series and the initial one which, to a large degree, consisted of unknowns.

In view of this and the negative reports, it was concluded that the reaction is not suitable or not sufficiently well defined. Therefore, some attention was directed toward the investigation of specific reactions which might account for the mechanism, and consideration was given to reducing properties of the chorionic gonadotropic hormone. At that time the carbohydrate content of this hormone had not been established and interest was turned in particular to its rather unusual properties of taking up iodine at a greatly increased rate in the presence of a relatively large amount of phosphate buffer salts at moderately elevated temperature.[16]

This behavior was traced to the phenolic groups present in the hormone and in nearly all proteins.[17] In one series of normal specimens free of detectable protein, it was found that pregnancy and nonpregnacy specimens could be differentiated.[18] Similar findings have been reported by Mello.[19] Nevertheless, while the reaction is quite sensitive, the presence or variations of minute quantities of ordinary proteins would obviously interfere. Numerous attempts at separating the desirable and undesirable fractions were made without success, employing procedures which might be practical in routine work.

Therefore, from these considerations and from the data briefly presented here, it must be concluded that at present a suitable means for the chemical determination of pregnancy based upon the reducing properties of gonadotropin, if feasible, has not as yet been adequately defined. However, it is believed that a study of the phenolic reaction first observed in this work may have wider application in view of the functional dominance of this radical in a number of hormones, enzymes, and proteins of disease.

References

1. Mello, M. I.: Rev. brasil. de biol. **3**: 119, 1943.
2. Somogyi, M.: J. Biol. Chem. **117**: 771, 1937.
3. Visscher, J. P., and Bowman, D. E.: Proc. Soc. Exper. Biol. & Med. **31**: 460, 1934.
4. Belonoschkin, B.: Zentralbl. f. Gynäk. **61**: 2797, 1937.
5. Messinger, W. J., Presberg, M. H., and Fellows, M. D.: Am. J. Obst. & Gynec. **35**: 295, 1938.
6. Bodo, B.: Orvosi hetil. **81**: 11, 1937.
7. Frankl, O., and Engel, P.: Zentralbl. f. Gynäk. **60**: 2645, 1936.
8. Ostadal, B.: Zentralbl. f. Gynäk. **61**: 266, 1937.
9. Dodds, G. H.: Brit. M. J. **2**: 244, 1936.
10. Menken, J. G.: Nederl. tijdschr. v. geneesk. **79**: 979, 1935.
11. Dolff, C.: Zentralbl. f. Gynäk. **59**: 2901, 1935.
12. Friedrich, B.: Monatschr. f. Geburtsh. u. Gynäk. **103**: 211, 1936.
13. Patkay, K.: Arch. f. Gynäk. **169**: 13, 1939.
14. Frech, H. C., Jr.: Am. J. Obst. & Gynec. **33**: 854, 1937.
15. Frech, H. C., Jr.: J. M. A. Georgia **27**: 240, 1938.
16. Bowman, D. E.: J. Biol. Chem. **137**: 293, 1941.
17. Bowman, D. E.: J. Biol. Chem. **141**: 877, 1941.
18. Bowman, D. E.: J. Lab. & Clin. Med. **24**: 1072, 1939.
19. Mello, M. I.: Rev. brasil. de biol. **2**: 343, 1942.

HYPERNEPHROID CARCINOMA OF THE KIDNEY OR ADRENAL (?) AND PREGNANCY*

A. F. LASH, PH.D., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Michael Reese Hospital)

THE literature dealing with renal tumors as a complication of pregnancy is extremely scarce, and one may conclude that such a condition is so rare that it may be termed a clinical curiosity (Adair and Stieglitz). Stoeckel, Marz, Kneise, Braatz and Parkes have reported instances in which they removed malignant unilateral growths during pregnancy without causing abortion and with spontaneous normal outcome at term.

This group of tumors, hypernephroid carcinoma (or clear-cell adenocarcinoma) are familiar to all pathologists, but they are so peculiar in their histological characteristics and location that there is no unanimity of opinion as to their origin. They are recognized clinically by their symptoms of hematuria, pain, and tumor in the loin. But only one of these symptoms may be present at one time. Pregnancy is influenced by them only as a mechanical factor producing pressure on the kidney or ureters. The tumor may be stimulated in its malignant growth during pregnancy (Wagner).

A point I wish to make is the frequency with which the surgeon misses uterine, adnexal, and extrapelvic masses at the time of lower uterine segment cesarean section, because the operative field is restricted to the lower uterine segment. Occasionally bicornuate uteri, fibroids, and ovarian neoplasms are overlooked, and certainly extrapelvic masses are totally ignored. With proper precaution, I would suggest the careful palpation of the fundus and adnexa.

The following case report of a hypernephroid carcinoma of the kidney or suprarenal associated with pregnancy is therefore of clinical interest.

A. M., a 30-year-old white primigravida, entered the Michael Reese Hospital on June 7, 1944, because of hypertension and albuminuria with a pregnancy at term. Her prenatal observation began on Oct. 29, 1943, when she was eight weeks pregnant. At that time blood pressure was 122/80. Physical status and urinary findings were normal. During the course of her pregnancy she had transient rises of the systolic blood pressure varying from 148 to 172 but always resuming a normal level after rest, restricted diet, and elimination. She gained 18 pounds and had no pathologic urinary findings. Her past history was entirely negative.

On admission, the physical examination revealed a nervous, apprehensive individual with the findings of a full-term pregnancy. Her weight was 133 pounds. Blood pressure was 182/100. Urinalysis showed 2 plus albumin. Blood examination showed 3,860,000 erythrocytes, 5,450 leucocytes, with 85 per cent hemoglobin. Nonprotein nitrogen was 25 mg. and uric acid 4.5, per 100 c.c.

She was under a strict regime of bed rest, low-protein, salt-free diet, daily magnesium sulfate, and sedation. Since no improvement occurred and medical induction of labor failed, the interruption of pregnancy was considered.

On June 10, 1944, with the indication of a persistent pre-eclampsia, a lower uterine segment cesarean section was performed under local anesthesia, and a normal male child, weighing 3,120 grams (6 pounds, 14 ounces), was delivered. The postoperative course was uneventful and afebrile until the seventh postpartum day, when she complained of right abdominal pain, and the temperature rose to 102.4° F. with a pulse rate of 88. Her blood count showed 4,000,000 erythrocytes, 10,800 leucocytes, and 90 per cent hemoglobin. The urine contained 1 plus albumin. On physical examination a large cystic mass was found in the right upper quadrant of the abdomen with a medial tubular mass. The tentative diagnosis was torsion of a right ovarian cyst or an acute cystic degeneration of a pedunculated fibroid.

*Presented before The Chicago Gynecological Society, Oct. 20, 1944.

Two days later the blood examination showed erythrocytes 3,850,000, leucocytes 15,600, and hemoglobin 65 per cent. On repeated examination the mass remained high in the right upper quadrant and fixed, not moving with respiration. Therefore, an extrapelvic, retroperitoneal neoplasm was considered.

A consultant, Dr. M. L. Parker, a general surgeon, saw the patient on June 19, the ninth postoperative day, and his notes were:

"The exact diagnosis is not clear at this time. A high ovarian cyst is possible; a retroperitoneal tumor must also be considered. In view of the fever, relative comfort of the patient, absence of ileus, and reflex symptoms, conservative therapy is suggested."

To obtain further new information, an intravenous urography was done and reported as follows:

"A survey film followed by excretion urography revealed the following: There is a normal bilateral thrust excretion at five minutes, with progressive excretion from both kidneys at fifteen and thirty minutes. The right kidney is shown to be markedly displaced to the left, the renal pelvis actually protruding slightly to the left of the spine, crowded over by a large mass in the right lumbar region. The ureter on the right side from the ureteropelvic junction down to the sacroiliac is markedly dilated, indicating partial obstruction, probably due to pressure from the tumor mass. In the lateral view the right kidney is shown to be displaced somewhat anteriorly but the calices appear within normal limits. The left kidney appears normal throughout as to size, configuration and the renal pelvis.

"Conclusions: There is nothing characteristic about this mass to identify it except that it produces marked displacement of the right kidney. The possibility, however, of a perinephritic abscess or of a retroperitoneal tumor must be considered." (Fig. 1.)

Fig. 1.

The patient's febrile course remained the same. The blood count now was 2,970,000 erythrocytes, 10,200 leucocytes, and 50 per cent hemoglobin, so a transfusion of 500 c.c. of whole blood was given. Sulfadiazine (90 grains daily) given over five days followed by three days of penicillin (100,000 units daily) produced no change in the febrile course. Pelvic examination showed a well-involuted uterus with no pathologic findings in either the adnexa or broad ligaments. Since no change had occurred in the clinical course regardless of therapy, surgical exploration was considered desirable.

On July 15, 1944 (thirty-five days postcesarean section), with the following findings: blood pressure 112/70, erythrocytes 3,890,000, leucocytes 12,600, and hemoglobin 62 per cent,

exploratory laparotomy was undertaken by Dr. M. L. Parker. Spinal anesthesia supplemented by cyclopropane was used. With an aspirating needle, about 400 c.c. of dark, brownish-red thin fluid was obtained. A right upper abdominal incision was then made. Upon entering the peritoneal cavity, a large retroperitoneal mass was found which had pushed the ascending colon medially and superficially. The ascending colon was adherent to the mass. After freeing the colon, the parietal peritoneum over the mass was incised. The mass originated from the upper portion of the right kidney. By dull dissection the mass was freed from the surrounding areolar tissue bed and when excised from its origin the upper one-third of the kidney was separated from the lower two-thirds, requiring several mattress sutures. No other adrenal gland was observed. The peritoneum was closed and the right kidney fixed. A Penrose drain was inserted through a stab wound in the right subcostal region and the abdomen was closed in layers in the usual manner. The patient tolerated the operation well and made an uneventful recovery, going home on the fifteenth postoperative day (fifty days after her cesarean section).

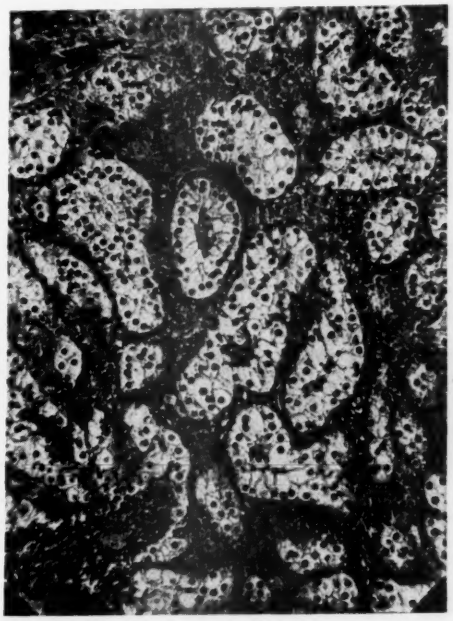

Fig. 2.

The pathologic examination by Dr. Otto Saphir was reported as follows: "The specimen consists of a thick-walled saccular structure measuring 18 cm. in diameter in the collapsed state. The wall measures up to 1.5 cm. in thickness and is grayish white. The lining is ragged yellow or pink. The lumen is filled with friable spongy yellowish-red material. Microscopic examination shows hypernephroid carcinoma (clear cell adenocarcinoma) with tremendous hemorrhage and necrosis and the formation of cystlike hematoma." (Fig. 2.)

References

1. Adair, F. L., Ryerson, M. C., and Stieglitz, E. J.: Obstetric Medicine, Philadelphia, 1934, Lea & Febiger, p. 580.
2. Braatz, E.: Deutsche Ztschr. f. Chir. **48**: 56, 1898.
3. Kneise, O.: Zentralbl. f. Gynäk. **54**: 292, 1930.
4. Marz (Quoted by Schmidt, L. E.): Surg., Gynec. & Obst. **21**: 679, 1915.
5. Parkes, C. T.: Am. J. M. Sc. **100**: 257, 1890.
6. Stoeckel, W.: München. med. Wchnschr. **71**: 257, 1924.
7. Wagner, G. A.: Ztschr. f. Geburtsh. u. Gynäk. **59**: 338, 1907.

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LEIOMYOMA OF THE OVARY COMPLICATING PREGNANCY

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(From the Grand Forks Clinic)

AN EXTENSIVE search of the literature has revealed only two instances of leiomyoma of the ovary complicating pregnancy. As far as is known, the present case is the third to be reported.

R. Olshausen[1] reported the case of a nullipara, aged 38 years, married for fourteen years, who came under his observation early in September, 1893. The abdomen had increased markedly in size and the patient suffered considerable discomfort, including beginning respiratory disturbances. Examination under anesthesia revealed a tumor, almost as large as a man's head, which lay half in the pelvis and half above it. The uterus lay entirely outside the true pelvis and was greatly displaced toward the right and forward. A second tumor, more irregular and more nodulated, also somewhat smaller than the one at the left, was located above the uterus and seemed to be connected with the latter. There was no ascites.

Operation was performed on Sept. 16, 1893. The tumor on the left side was lifted out of the pelvis with difficulty and had a firm pedicle, the thickness of a man's thumb. The tumor at the right had a pedicle which was attached several centimeters behind and above the right ovarian ligament. The uterus seemed to be pregnant in the third month. Both tumors were myomas, of both ovaries, but the microscopic findings were not given. One of them weighed 960 grams and the other 650 grams. Convalescence was undisturbed. On March 21, 1894, the patient gave birth to a mature living child. Manual detachment of the placenta was necessary. The puerperal period was normal.

Brachetto-Brian and Casco[2] reported the case of an unmarried 17-year-old girl with antecedents of dysmenorrhea and without antecedents of pregnancy who was operated upon in emergency for pelvic appendicitis. During the operation the appendix was found healthy but there was a massive intraperitoneal hemorrhage. The left ovary was removed, and its histologic study established the diagnosis of pregnancy in the cortical zone of an organ showing generalized endometriosis. The embryo was not found. No ovarian tissue was found, but it was replaced by a fibroleiomyomatous fabric. The authors concluded that the ovary in which the impregnated ovum was implanted showed a double alteration: generalized endometriosis and fibroleiomyomatosis.

Report of Case

Case No. 33867. A married white woman, 34 years of age, registered at the Grand Forks Clinic on Feb. 24, 1944. She had been married four and one-half years and this was her first pregnancy. Her last menstrual period began on Dec. 6, 1943, and her estimated date of confinement was Sept. 12, 1944. There was nothing remarkable in her antecedent history except that her previous failure to conceive had been involuntary and one year earlier she had been told, elsewhere, that she had a pelvic tumor. According to the patient, this tumor had not been found on subsequent examinations. Her chief complaints were soreness in the lower abdomen, a rapid increase in size of the lower abdomen and premenstrual sensations. Menstruation had become established at 14 years, 28-day cycle and 5 days of moderate flow.

General physical examination was not remarkable except for a soft basal systolic murmur, transmitted to the apex and, faintly, to the left axilla. Temperature was 99°F., pulse rate 100, respiratory rate 16, and blood pressure, 130/90.

There was a hard tumor on the right side of the lower abdomen, rising two-thirds of the distance to the umbilicus and moderately tender. A depression occurred in the lower mid-abdomen between this tumor and a softer mass to the left of the midline, which was comparable in size to a three months' pregnancy. The breasts were large, globular, and

engorged. The introitus was nulliparous and marital. There was a firm, hard tumor blocking the posterior cul-de-sac and a harder tumor above this and to the right. The mass in the posterior cul-de-sac could not be displaced. The cervix was high under the left pubic ramus and what appeared to be a pregnant uterus was crowded to the left side of the lower abdomen.

A soft tissue roentgenogram of the lower abdomen showed no fetal parts but increased density on the right side.

The value for hemoglobin was 72 per cent with the 17-gram Sahli tube; erythrocytes numbered 3,630,000, leucocytes, 15,200, and Kahn and Kolmer tests were negative. The sedimentation rate was 49 mm. in one hour. The differential blood count was not remarkable. The urine showed a heavy trace of sugar and the sediment showed an occasional leucocyte and erythrocyte.

She was admitted to St. Michael's Hospital in Grand Forks with a diagnosis of pelvic tumor complicating pregnancy; probably ovarian tumor. On Feb. 25, 1944, the abdomen was opened through a right lower paramedian incision. A solid tumor of the right ovary was delivered into the wound with some difficulty and a right ovariectomy was performed. There was a hard, subserous myoma on the anterior uterine wall which was showing evidence of necrosis and this was removed and the uterine wound was closed with fine plain catgut on an atraumatic needle. The abdomen was closed in layers with 00 plain and 00 chromic catgut, three silkworm tension sutures were inserted, and the skin was closed with Nylon. The anesthetic was ethylene-oxygen-ether vapor.

Fig. 1.

Gross Pathology.—A solid tumor of the right ovary, incarcerated in the pelvis, and weighing 1,170 grams. It measured 16 cm. in length and 13 cm. in width. Its lengthwise circumference was 43 cm. and its narrowest circumference, 31 cm. The surface was nodular but the covering was smooth and there was no evidence of implants. On section, the tumor appeared hard except for one softened area, 3 by 2 cm., near the superior surface.

The uterus was approximately the size of a three months' pregnancy and on its anterior surface was an acorn-sized subserous myoma. Several smaller "seedling" subserous myomas were present but were not disturbed. The uterus was crowded to the left of the midline and occupied the left lateral pelvic cavity, due to the pressure of the tumor in the right ovary. The left ovary was about twice the normal size and contained several follicular cysts. A corpus luteum was not positively identified. Both Fallopian tubes appeared grossly normal and were preserved. The veins of the right broad ligament were considerably engorged.

The entire specimen was fixed in formalin and sent to Dr. E. T. Bell. His report is as follows: "The ovary is entirely replaced by a massive hard tumor roughly spherical in

shape and varying in diameter from 10 centimeters to 12 centimeters. The outer surface is smooth except for a few coarse nodular elevations. On section the growth is of hard fibrous texture with no soft areas and no cysts. Microscopically the tumor is of uniform structure throughout. It is composed of adult smooth muscle with a moderate amount of collagenous tissue between the muscle fibers (Fig. 1). The diagnosis is a benign leiomyoma."

Postoperative Course.—The immediate postoperative condition of the patient was excellent, but late in the afternoon of the day of operation she began to pass blood clots from the vagina. Progestin therapy was started with the intramuscular injection of Lipolutein,* 5 mg. every four hours for the first two postoperative days, then at longer intervals until the sixteenth and final injection was given on the eighth postoperative day. There was no bleeding after the third postoperative day. Her maximum temperature was 100.6°F. on the afternoon of the day of operation. She was discharged on the fourteenth postoperative day.

Regular prepartum examinations between April 16, 1944, and Aug. 16, 1944, showed the pregnancy to be developing normally. On Sept. 1, 1944, her obstetrician, Dr. Roger H. Mattson of McVille, North Dakota, delivered her of a boy weighing 7 pounds, 8 ounces following an uneventful labor. Her postpartum course was normal.

Summary

A case of leiomyoma of the ovary complicating pregnancy is reported. A search of the literature revealed only two other cases where this type of ovarian neoplasm has been found in association with pregnancy.

References

1. Olshausen, R.: Veit's Handb. d. Gynäk. ed. 2, 1: 788, 1907.
2. Brachetto-Brian, D., and Casco, C. M.: Rev. Asoc. méd. argent. 55: 375, 1941.

*Parke, Davis & Company.

HEMINECROSIS OF CERVICAL STUMP FOLLOWING SUPRAVAGINAL HYSTERECTOMY

ROBERT T. FRANK, A.M., M.D., NEW YORK, N. Y.

MRS. M. S., a 39-year-old nullipara, had known of the presence of uterine fibroids for seven years. She was referred to me because of increasing menstrual bleeding prolonged to from seven to nine days.

The patient was somatically normal. The genital tract was nulliparous, uninfected. The uterus was enlarged to the size of a four months' pregnancy and distorted by multiple myomas which mainly were retrocervical.

On June 8, 1942, a supravaginal hysterectomy for fibroids, right salpingo-oophorectomy for closed hematosalpinx, and appendectomy were performed. No difficulties were encountered.

The early postoperative convalescence was unusually smooth and afebrile. On the tenth day slight bleeding from the vagina was noted. On the eleventh day, profuse bleeding, chilly sensations, temperature elevation to 103.6° F. white blood count 19,000, and polynuclear count 60 per cent developed. No peritoneal symptoms existed. Sulfadiazine by mouth was prescribed.

On pelvic examination an enlargement of the portio was felt. By speculum examination a sharply demarcated necrosis of the right side of the cervix could be seen. The affected area was swollen, purple, and elevated. The process extended into the right fornix. (Fig. 1, *A*).

One June 21, the thirteenth day following operation, the entire necrotic area was readily removed as a slough, exposing a raw depression in the lateral fornix close to the course of the right ureter and uterine artery (Fig. 1, *B*). A packing of iodoform gauze was inserted lightly against the defect. Temperatures were from 99° to 100° F. No secondary hemorrhage developed. The patient was discharged well and fully healed on the twenty-second day. Fig. 1, *C* shows completed cicatrization as observed six months after operation. There was a minimal scar in the right fornix.

A. *B.* *C.*

Fig. 1.—*A*, View of portio vaginalis through speculum. The right half is swollen, bluish-black in color. *B*, Diagrammatic transverse section showing extent of necrosis into right vaginal fornix. *C*, View of healed portio six months after operation. Defect and scar.

Comment.—At operation both ligatures to the uterine arteries were applied identically and at the same level. Presumably the descending vaginal vessels on the right side were anomalous and did not possess the customary free anastomosis with the ascending vaginal vessels. Consequently, the affected area (right half of the portio, right fornix) was rendered ischemic and sloughed off (dry gangrene). If the process had been due to thrombosis and infection, further extension into the fornix with secondary hemorrhage from the uterine artery might have occurred. In anticipation of such an eventuality the patient was watched incessantly and her blood typed.

A SIMPLE TECHNIQUE TO TEST TUBAL PATENCY

ALBERT DECKER, M.D., F.A.C.S., NEW YORK, N. Y.

THE production of pneumoperitoneum by the transuterine route is evidence of tubal patency. The method introduced by I. C. Rubin for testing tubal patency provides for the introduction of air or CO_2 under pressure into the abdominal cavity through the uterotubal channels. Refinements in diagnosis are provided by precise readings registered by kymographic tracings of the pressure during the insufflation. The simplest apparatus for tubal insufflation utilizes a bulb syringe, atmospheric air, and an intrauterine cannula. All methods so far used rely upon positive pressure exerted by air or CO_2, the latter being more satisfactory because of its rapid absorption time. The pressure is exerted through an intrauterine cannula while the patient is in the lithotomy position. Instances of air embolism have been reported after the insufflation of unduly high intrauterine pressures, and when air had been used for the insufflation.

Recent personal observation reveals that pneumoperitoneum can be produced by utilizing the negative intra-abdominal pressure created

by assuming the knee-chest posture. This method is safer and requires only such instruments as are usually available in the physician's office.

Technique

The patient is placed in the knee-chest posture. The perineum is elevated with a Sims speculum. The cervix is exposed, painted with merthiolate, grasped with a tenaculum, and an intrauterine cannula or metal catheter is introduced into the uterus. Because of the negative intra-abdominal pressure, an immediate pneumoperitoneum results if the tubes are patent. The amount of air entering the abdomen is usually about 150 to 300 c.c. as demonstrated by x-ray or fluoroscope. The characteristic shoulder pain and symptoms of pneumoperitoneum occur on resumption of the sitting or standing position. The negative pressure created in the abdomen by the knee-chest posture, as measured by the Zavod Aneroid Pneumo* apparatus, attains 8 to 12 c.c. of water.

Pneumoperitoneum may be produced after slight dilatation of the cervix with a cervical dilator and without introducing a cannula, with the patient in the knee-chest posture.

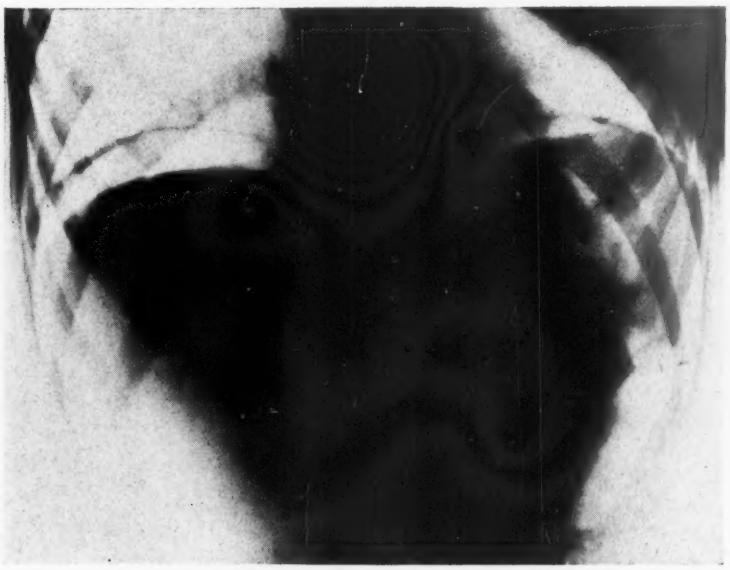

Fig. 1.

This method has several advantages; very few instruments are needed, the air enters the abdomen only if the tubes are patent, not spastic, and as a result of negative pressure created beyond the distal end of the oviduct. The pressure within the uterine cavity and tube is never elevated. The danger of air embolism is reduced. Other accidents are avoided that result from high intrauterine and intratubal pressure. When pneumoperitoneum results from the knee-chest posture, after introduction of the cervical cannula, at least one tube may be considered quite normal.

Because of the simplicity of this method, it is suggested as the initial procedure in the determination of tubal patency. A positive result will make other procedures unnecessary. This method does not allow for some diagnostic details that can only be gained by more elaborate apparatus, and it cannot be relied upon as a therapeutic measure to overcome obstruction of the oviduct. It does not offer the diagnostic detail or therapeutic effect of high intrauterine pressure, but, on the other hand, it is free from its dangers.

*Manufactured by the American Cystoscope Makers, 1241 Lafayette Avenue, Bronx, New York.

Example.—Mrs. M. J., 32 years old, white, married ten years, with one child 4 years old, had had a normal delivery. The postpartum period was prolonged (twenty-two days) because of abdominal pain, bleeding, and slight temperature.

Menstrual onset occurred at 14 years of age, was regular every twenty-eight days, duration four days. Menstruation was resumed six weeks following childbirth and has been regular since. There was no vaginal discharge.

Her weight is 130 to 134 pounds constant.

Patient has not been pregnant since birth of child four years ago, although having regular intercourse. She has never used any method of contraception. Pregnancy is now desired.

Vaginal examination was entirely negative. Because of obstetric (postpartum) history of possible infection, tubal occlusion was suspected.

The patient was placed in knee-chest posture and an intrauterine cannula was inserted through the cervix. An immediate pneumoperitoneum resulted as shown by x-ray (Fig. 1).

10 West 74th Street

Necrology

WILLIAM HANS VOGT, M.D., Professor and Director of the Department of Obstetrics and Gynecology, St. Louis University, died suddenly of heart disease at Atlantic City, New Jersey, June 17, 1945, at the age of 68, while attending as examiner a meeting of the American Board of Obstetrics and Gynecology. Born in St. Louis in 1877, he graduated from the Missouri Medical College (now Washington University), did postgraduate work in Vienna under Shauta, and Hitchman, and in Dresden under Leopold. Dr. Vogt was associated with various hospitals in St. Louis as an attending and consultant and was certified as a Diplomate of the American Board in 1932. He was a Fellow of the American College of Surgeons and a member of the American Association of Obstetricians and Gynecologists, the Central Association and Southern Medical Society, as well as a member of the Advisory Editorial Board of the American Journal of Obstetrics and Gynecology.

Department of Reviews and Abstracts

Selected Abstracts

Menstruation, Dysmenorrhea, Etc.

Whitacre, Frank E., and Barerra, Benjamin: War Amenorrhea, J. A. M. A. **124:** 339, 1944.

The authors report their findings among 1,172 women interned at the Santo Tomas Internment camp in Manila, Philippines. Among this group there were 125 patients with amenorrhea which had developed since the outbreak of the War. It was felt that nutritional factors had little to do with the sudden onset of this widespread condition, and that the amenorrhea observed was probably due to severe psychic shock, worry, and fear, which, acting through the autonomic nervous system, caused a complete suppression of ovarian function. Active treatment consisted of the administration of estrogenic substances, vitamin E, and reassurance.

WILLIAM BERMAN.

Hartman, Carl G.: The Normal and the Hyperactive Ovary in the Menstrual Cycle and in Hyperplasia, West. J. Surg. **52:** 139, 1944.

Menstruation is a function limited to man, monkey, and the apes. Six types of nontraumatic bleeding must be distinguished: postpartum, abortion, placenta sign, intermenstrual, menstruation without ovulation, menstruation after ovulation. Non-ovulatory menstruation is seasonal in the monkey and is a common occurrence in women, even normal women. This menstruation is indistinguishable from that occurring following ovulation. In both cases uterine bleeding and the desquamation of tissue is the result of estrogen deprivation. Apparently the withdrawal of the estrogens is the essential factor in the induction of menstruation. Progesterone is not essential to the process.

In the monkey, long-continued pathologic bleeding practically always is associated with a small hypoplastic uterus. Bleeding, however, can be produced from a hyperplastic endometrium by a long-continued administration of the estrogens. Small doses over long periods are required, single large doses do not produce hyperplasia. Hyperestronization by endogenous estrogens from persistent follicle cysts in the monkey can produce hyperplasia with bleeding. These persistent follicles can occasionally be associated with ovulation from the opposite ovary. Normal menstruation, ovulatory or anovulatory, may occur in the presence of large follicle cysts, but the persistence of the cysts may result in complete destruction of the involved ovary. Fluid aspirated from these cysts is low in estrogen and again it is emphasized that it is long-continued stimulation of the endometrium by small doses of estrogen that brings about hyperplasia.

WILLIAM BICKERS.

Wollner, A.: The Menstrual Cycle in the Human Cervical Mucosa and Its Clinical Significance, Am. J. Surg. **52:** 331, 1942.

The author has observed cyclic changes in the mucosa of the cervix corresponding to that of the endometrium in 70 per cent of the cases studied. He believes that the estrogenic hormone acts upon the cervix in the same way that it acts upon the endometrium. He states that he has been able to reproduce "erosions" of the cervix in menopausal women by the injection of estrogen, and that these disap-

peared when the administration of the material was discontinued. Epithelial metaplasia in the endocervix is interpreted not as evidence of a healing erosion but rather as the result of hormonal stimulation. The importance of this hormonal etiology lies in a possible relationship to the development of carcinoma.

FRANK SPIELMAN.

Gubner, Richard, and Ungerleider, Harry E.: Vitamin K Therapy in Menorrhagia, South. M. J. 37: 556, 1944.

The liver is intimately concerned with the conjugation of the estrogenic hormone for excretion. Impairment of liver function will impair the estrogen inactivating capacity and therefore permit abnormally high estrogen levels in the blood. This may produce gynecomastia, endometrial hyperplasia, premenstrual tension, and perhaps dysmenorrhea. Disturbance in liver function may also interfere with the production of prothrombin and thus retard or actually prevent the clotting of blood. The authors report on a group of patients with prolonged menstrual flow who were treated with Vitamin K for the purpose of raising their prothrombin level and thus controlling their menorrhagia by promoting clot formation. The duration of flow was reduced in approximately one-half of the patients treated.

Prothrombin studies were not carried out on all these patients. However, in two cases it was found that the prothrombin time was prolonged and the Vitamin K therapy beneficially influenced the menorrhagia in these cases.

WILLIAM BICKERS.

Nogueira, Nelson G.: Premenstrual Tension, An. brasil. de ginec. 18: 47, 1944.

The author recalls the theories of Frank (deficient renal excretion of estrogens during the days preceding menstruation causes their retention in the blood, influencing the sympathetic nervous system and producing the symptoms), of Israel (presence of nonantagonized estrogens) and of Greenhill and Freed who maintain that increase in interstitial fluids, caused by retention of the sodium ion by the ovarian steroids, is the mechanism of the various premenstrual disturbances. The increase in the tissue fluid may be slight or lead to great edema, and the symptomatology would depend on the variable fluid distribution through the involved organs. Greenhill and Freed recommended abstention from salt in the food during the last two weeks of the menstrual cycle and the daily use of 1.80 Gm. of ammonium chloride divided into three doses.

The change in the water metabolism is evident and all the factors which interfere with it must be studied carefully. They are characteristically altered in normal pregnancy and more markedly in edema associated with pregnancy. Some of these changes are also found in the menstrual cycle, and perhaps some constancy in these variations could be discovered which might explain premenstrual tension.

J. P. GREENHILL.

The Newborn

Potter, Edith L.: The Lessons to Be Learned From a Study of Infant Deaths, J. A. M. A. 124: 336, 1944.

Analysis of statistics shows that there are three principal channels into which efforts to reduce deaths in the neonatal period should be directed. These are prematurity, birth trauma, and infections. Since no one has been able to prevent the premature onset of labor, except in isolated cases, it is necessary to improve the environment into which the premature infant is born if its chances of survival are to be increased. Reduction of birth trauma can be counteracted by improved training of the obstetrician. The third principal factor is infections, and an attempt should be made to eliminate all pathogenic bacteria from the environment of the infant during delivery and after birth.

WILLIAM BERMAN.

Wessel, Morris A.: Chylothorax in a Two-Week-Old Infant With Spontaneous Recovery, J. Pediat. 25: 201, 1944.

Chylothorax is a relatively rare condition which may occur at any age. Most cases are believed to result from rupture of the thoracic duct itself, or from one of its tributaries, although not necessarily so.

A case of chylothorax in a 14-day-old infant is presented. The patient recovered following repeated aspiration of the right pleural cavity, for relief of recurrent respiratory difficulty. A brief review of the literature dealing with this entity is included.

JAMES P. MARR.

Halbrecht, I.: Role of Hemoagglutinins Anti-A and Anti-B in Pathogenesis of Jaundice of the Newborn (Icterus Neonatorum Precox), Am. J. Dis. Child. 68: 248, 1944.

The author found among 10,000 births only nine cases of true erythroblastosis; there was a mortality of 60 per cent.

Lenart and Biro stated that hemoagglutinins are the cause of all icterus in the postnatal period. The author is in disagreement and is convinced that agglutinins anti-A and anti-B cause only icterus precox, and not the usual physiologic icterus which does not appear until twenty-four hours after birth.

The placental blood on these newborn infants showed 1.75 mg. bilirubin content, as contrasted against 0.75 mg. in physiologic icterus and 0.55 mg. per 100 c.c. in children without icterus.

The passage of these agglutinins from the mother to the fetus by way of the placenta has been demonstrated by Hirszfeld and Zborowski and others, who showed that in 30 per cent of newborn children it is possible to find hemoagglutinins which disappear from the blood after a short time. The agglutinins anti-A and anti-B are milder hemolytic agents for the newborn than the agglutinins anti-Rh, for the former are absorbed by the antigen secreted by the tissues, while the latter is absorbed only by the red blood cells, the Rh factor being present only in the erythrocytes and not in the tissues.

Of special interest was the determination of the blood group of the infants with icterus precox and their mothers. Fifty-seven of the 60 infants, or 95 per cent, had blood incompatible with that of the mother, so that the serum of the latter agglutinated the red cells of the former. A group of 160 infants with physiologic icterus revealed that 30 per cent had blood incompatible with that of the mother, while of 2,000 infants with icterus, only 26.5 per cent showed incompatibility.

JAMES P. MARR.

Blatt, Maurice L., Zeldes, Mary, and Goodfriend, James: Epiphysial Dysgenesis Associated With Cretinism in a Premature Infant, Am. J. Dis. Child. 67: 480, 1944.

In roentgenograms, epiphysial dysgenesis is diagnosed by the appearance of multiple small irregular islets of calcification, scattered over a considerable area. The islets are irregularly spaced, and the anatomic distribution does not conform to that of the normal centers of ossification.

It is not to be confused with osteochondritis deformans, which is generally accompanied by pain and does not respond to thyroid therapy. The authors report such a case.

JAMES P. MARR.

Anderson, Nina A., Sage, Dorothy N., and Spaulding, E. H.: Oral Moniliasis in Newborn Infants, Am. J. Dis. Child. 67: 450, 1944.

This study was undertaken to investigate further some of the factors which may be related to the incidence, the source, and the spread of oral moniliasis in newborn infants.

Vaginal swabs were obtained from 57 of the mothers during labor, and at delivery. The occurrence of oral thrush in 6 of 13 infants whose mothers had *Monilia*

albicans in the vaginal flora is significant when compared with the incidence of oral thrush in only 4 of 38 infants from whose mothers' vaginal swabs Monilia was not isolated, and in only 5 of the 44 infants from whose mothers either no species of Monilia was obtained or only forms other than *M. albicans.*

The interval between the birth of the infant and the cultural demonstration of the presence of *M. albicans* in the infant's mouth averaged three days in those instances in which the mother had vaginal mycosis, in contrast to six and two-thirds days when the mother's vaginal swab failed to show Monilia.

The authors recommend that all infants whose mothers reveal a vaginitis due to *M. albicans* be isolated as a prophylactic measure. Also, that it is important to diagnose and treat all such mothers ante partum in order to reduce the possibility of the transfer of the infection to the newborn infant.

JAMES P. MARR.

Pregnancy, Physiology, Diagnosis

Landgrebe, F. W., and Samson, L.: The Hogben Pregnancy Test With a Note on the Breeding of the Xenopus for the Test, J. Obst. & Gynaec. Brit. Emp. **51:** 133, 1944.

The frog test (Hogben) for pregnancy, according to the authors, is as reliable as any other test, provided at least ten days elapse since the first missed period. The authors did 258 tests for pregnancy using the Scott technique for the extraction of the urine. Two hundred and twenty have been checked against ultimate clinical findings and, except in two cases where the patient showed menopausal symptoms, were found correct. At 22° C. a result is obtained within eighteen hours and the animals require feeding and cleaning only once a week. Each toad was used over twenty-four times and still responds satisfactorily. Laboratory bred Xenopus can be used for the test and is capable of producing a second generation which will also respond to pregnancy urine extracts.

WILLIAM BERMAN.

Corbit, J. D.: The Effect of Pregnancy Upon Experimental Hypertension in the Rabbit, Am. J. M. Sc. **201:** 876, 1941.

Fluctuations in the blood pressure, blood urea, and the excretion of urinary protein during pregnancy were studied in normal rabbits, and in rabbits in which arterial tension was previously raised by the experimental induction of renal ischemia. In both groups of animals it was found that pregnancy tended to produce a lowering of the systolic blood pressure a few days before the onset of labor. The return of pressure to the prepregnancy level occurred gradually during the first two to three weeks postpartum. In the normal animal there were no significant alterations of blood urea or protein-urea. In the renal ischemic animals, however, there was a slight prepartal fall of blood urea and a tendency toward the occurrence of protein urea.

The failure to produce an experimental result characterizing the features of the syndrome observed in clinical medicine is probably due to either the nature of the experimental hypertension in the animal being different from that seen in the childbearing woman, or the physiology of pregnancy in the animal differing in those factors which account for the blood pressure changes observed in human beings.

FRANK SPIELMAN.

Craig, A. A., Lewis, F. J. W., and Woodman, D.: Survey of Vitamin C Level in Wartime in Pregnant Women,, Brit. M. J. **1:** 455, 1944.

Craig and his co-workers report some observations of forty pregnant women with respect to the degree of vitamin C saturation. This study was done under wartime conditions, which produced a lack of fresh fruit and often some deficiency of vegetables. There was a wide variation in the degree of saturation, mostly on the low side. There was also a wide seasonal variation with a definitely greater saturation from June to October.

FRED L. ADAIR.

Moll, Jorge Neval: Use of Prostigmine as Pregnancy Test and to Correct Retarded Menstruation, Rev. de ginec. e d'obst. 38: 177, 1944.

The author states that prostigmine acting on the parasympathetic produces vasodilatation through stabilization of acetylcholine and causes hyperemia of the endometrium. Soskin, Hechter, and Wachtel have used it for the differential diagnosis of early pregnancy and, when they found it innocuous for the pregnant uterus, have extended its use to the correction of retarded menstruation. Their results were confirmed by various Brazilian authors.

The test is positive, i.e., it releases the flow in menstrual delays depending on neurovascular changes and in lactation amenorrheas, and is negative in pregnancy and amenorrheas depending on endocrinopathies. In the latter cases, the differential diagnosis is made through biologic tests. The author presents fifteen cases which demonstrate the value of the test.

J. P. GREENHILL.

Miscellaneous

Balasquide, L. A.: Malaria in Connection With Obstetrics and Gynecology, Bol. Asoc. méd. de Puerto Rico 36: 269, 1944.

The author calls attention to a rare and usually misinterpreted condition caused by malaria, namely, gangrene of the external genitalia appearing in small isolated spots on the labia or assuming alarming proportions. Malaria in infancy and childhood may also cause serious delay or arrest in development of the genital organs. A marked increase in the vaginal discharge of women with chronic adnexitis has also been observed during the febrile attack. Functional disturbances of the ovary are rather frequent, but sterility seems to be out of the question, at least in Puerto Rico.

The deleterious influence of malaria on pregnancy is generally accepted. Goch found that pregnancy is interrupted in 41.3 per cent of the cases. This is a slightly higher percentage than that observed in Puerto Rico. Various factors have been incriminated for the abortion, but it is probable that it is due to a combination of these factors. Eclampsia is more frequent in women with malaria. Immunity against the disease, supposed to be conferred by pregnancy, is a myth.

An acute attack of malaria may induce labor. Although, in general, labor proceeds in a normal manner, malaria sometimes leads to uterine inertia which prolongs considerably the first stage. Many of the secondary inertias of the uterus observed in Puerto Rico are of malarial origin. The atony which occurs during labor frequently leads to severe postpartum hemorrhages.

Involution is usually retarded. Sometimes it develops so imperfectly that it constitutes another cause of postpartum hemorrhage. The lochia is more abundant and of longer duration. When attacks of malaria occur during the puerperium, lactation may disappear temporarily to reappear after the attacks, but in smaller amount.

Children born of mothers with malaria have a much higher mortality rate than those of mothers without the disease. Generally, they suffer from malnutrition, debility, defects of development, and prematurity.

Quinine is not contraindicated in the treatment of malaria of the pregnant woman, but West has demonstrated that the administration of massive doses produces auditory defects in the child. The careful use of small doses immediately after labor helps involution of the genitalia.

J. P. GREENHILL.